A Method for Vaccine Effectiveness Surveillance with Application to the BA.1 and BA.2 sub-lineages of the Omicron Variant

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Overview

We propose a surveillance method for updating estimates of vaccine effectiveness (VE) against infection with an emerging COVID-19 variant using dynamic case-control sampling. The method uses routinely-collected genomic surveillance data and leverages published VE estimates against a previous variant to produce a stable estimate of VE without some of the limitations by other designs.

Background

- New COVID-19 variants arise frequently with different viral properties that can impact the effectiveness of existing vaccines.
- Public health officials must rapidly assess VE against new variants so that they can adjust mitigation measures.
- In vitro estimates of VE can be produced quickly but don't map directly to specific health outcomes.
- Obtaining reliable estimates of VE in vivo often involves conducting a prospective cohort or test-negative case-control study, both of which require large sample sizes and substantial time for cases to accumulate.
- Genomic sequencing is costly and typically only available for a subsample of positive cases.

Data

- SARS-CoV-2 positive specimens linked with vaccination registry.
- Associated demographic information for cases (age, sex, race, congregate care status, and zip-code based community risk classification).
- Only utilize first diagnosed infections in analysis.
- Data are collected and provided by the Rhode Island Department of Health (RIDOH).
- The method is based on cases for which genomic sequencing is available.
  - This minimizes mis-classification bias relative to methods implementing calendar-based classification.
  - Can be applied in settings where only a subset of cases are sequenced.

Methods

- **Notation**:
  - S denotes variant subtype, with S=0 corresponding to being uninfected, s_0 denoting the previous variant, and s* denoting the emerging variant.
  - V denotes vaccine status, with V=0 corresponding to being unvaccinated and V ∈ {1, 2, . . . , J} representing level of vaccination.
- **Objective**: Estimate VE against a variant s:

$$\mathrm{VE}_v(s) = 1 - \frac{P(S=s \mid V=v)}{P(S=s \mid V=0)} = 1 - \mathrm{RR}_v(s,0)$$

- VE can be expressed as an odds ratio when risk of infection is low:

$$\mathrm{VE}_v(s) = 1 - \frac{P(S=s \mid V=v)/P(S=0 \mid V=v)}{P(S=s \mid V=0)/P(S=0 \mid V=0)} = 1 - \psi_v(s,0)$$

- Now consider estimating VE against an emerging variant s* in a setting where reliable estimates of VE against a previous variant s_0 are available.

$$\psi_v(s^*,0) = \frac{P(S=s^* \mid V=v)/P(S=0 \mid V=v)}{P(S=s^* \mid V=0)/P(S=0 \mid V=0)}$$

$$= \frac{P(S=s^* \mid V=v)/P(S=s_0 \mid V=v)}{P(S=s^* \mid V=0)/P(S=s_0 \mid V=0)} \times \frac{P(S=s_0 \mid V=v)/P(S=0 \mid V=v)}{P(S=s_0 \mid V=0)/P(S=0 \mid V=0)}$$

$$= \psi_v(s^*,s_0)\psi_v(s_0,0)$$

- Then, our estimator for $\mathrm{VE}_v(s^*)$ is:

$$\mathrm{VE}_v(s^*) = 1 - \psi_v(s^*,s_0)\psi_v(s_0,0)$$

$$= 1 - \psi_v(s^*,s_0)\{1 - \mathrm{VE}_v(s_0)\}$$

- **Methodological Considerations**:
  - Estimation of $\psi_v(s^*,s_0)$ from a sample of cases with sequenced virus, where selection into the sequenced sample is potentially nonrandom relative to the population of interest.
  - Uncertainty estimation from two sources: (1) uncertainty in estimate of VE against previous variant s_0 (2) uncertainty associated with. $\psi_v(s^*,s_0)$.
  - Potential differences in populations used to derive estimates of VE against previous variant and our study population.
  - Potential for differential transmissibility of emerging variant relative to the previous variant.

Vaccination Status	Adjusted BA.1 OR (95% CI)	Adjusted BA.2 OR (95% CI)
Unvaccinated	–	–
One Dose of Two-Dose Series	3.77 (2.72, 5.27)	5.13 (3.49, 7.58)
Completed Primary Series	1.90 (1.64, 2.20)	1.24 (1.02, 1.51)

Footnote to Table 2 (top of 3rd column):

[1] Estimated effectiveness ⩾ 7 months days after completion of primary vaccination series, Pfizer vaccine only.
[2] Moderna vaccine only
[3] Investigated Moderna and Pfizer vaccines separately, estimates shown are averages.
[4] > 120 days after completion of primary vaccination series, among individuals ages 12-59 years. Approximately 75% of samples were sequenced during the Delta-dominant portion of the study period.

Table 1: Estimates of $\psi_v(s^*,s_0)$ for the Delta variant compared to each of the BA.1 and BA.2 variants, produced using weighted logistic regression.

Results

Location	Study Type	# infections; # no infection	Primary Series VE, Delta (VE_j)	Primary Series VE, BA.1 (VE_j^*)	Primary Series VE, BA.2 (VE_j^*)
California[1] (Tartof *and others*)	cohort, Delta-dominant	197,535; 2,919,754	49 (46, 51)	3 (-13, 17)	37 (23, 48)
California[2] (Bruxvoort *and others*, 2021)	case control, sequenced	2,027; 10,135	87 (84, 89)	75 (69, 81)	84 (79, 88)
California (Tseng *and others*, 2022)	case-control, S-Gene Target Failure	26,683; 109,662	64 (60, 67)	31 (18, 42)	55 (44, 64)
Minnesota[3] (Puranik *and others*, 2021)	case control Delta-dominant	25,869; 25,869	59 (36, 75)	20 (-28, 52)	47 (15, 69)
Norway (Seppälä *and others*, 2021)	cohort, sequenced	5,430 4,199,429	65 (61, 68)	33 (21, 44)	56 (46, 65)
Denmark[4] (Gram *and others*, 2022)	cohort; Delta-dominant and sequenced	34,636 842,397	65 (64, 66)	33 (23, 43)	56 (47, 64)

Table 2: Estimated vaccine effectiveness against infection with the BA.1 and BA.2 sub-lineages, based on corresponding estimates of VE against infection with the Delta variant, for those with a complete primary vaccination series.

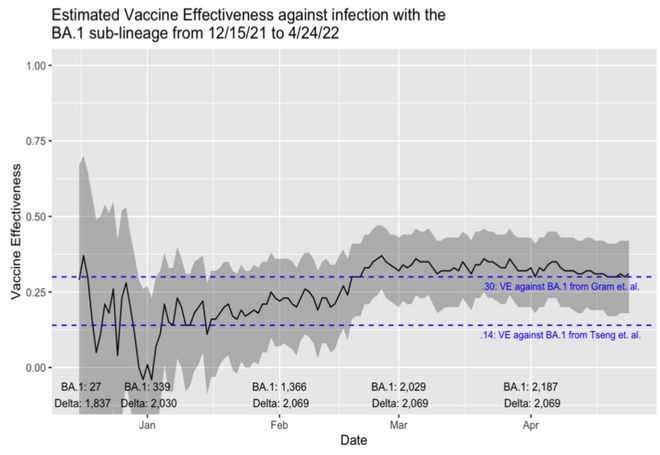

Figure 1: Estimates of VE produced using this method dynamically update and stabilize as cases accumulate.

Conclusion

- We can produce estimates of VE that stabilize quickly and are comparable in magnitude to results produced by other methods.
- We were able to detect reduced VE against each of the BA.1 and BA.2 sub-lineages relative to the Delta variant.
- Our estimates have large associated error, this could be reduced by sequencing a higher proportion of cases or implementing the method in a larger health department with access to more case records.
- **Limitations**:
  - The precision of our estimate partially depends on the precision of estimates reported in the literature.
  - We have assumed that estimates of VE against the previous variant are transportable to the Rhode Island population.
  - Sequencing delays can be substantial.

All analyses completed using R v4.0.2

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This study was classified as exempt by the RIDOH Institutional Review Board