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, S1 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:
  \[ \text{VE}(s) = 1 - \frac{P(S = s | V = 0)}{P(S = 0 | V = 0)} \]
  - VE can be expressed as an odds ratio when risk of infection is low:
  \[ \text{VE}(s) = 1 - \frac{P(S = s | V = 0)}{P(S = 0 | V = 0)} = 1 - \psi(s, 0) \]
• Now consider estimating VE against an emerging variant s* in a setting where reliable estimates of VE against a previous variant s0 are available.
  \[ \psi(s, 0) = \frac{P(s* | V = 0)}{P(s0 | V = 0)} \]
• Then, our estimator for VE(s*) is:
  \[ \text{VE}(s*) = 1 - \psi(s*, 0) \]

Methodological Considerations:
• Estimation of \( \psi(s*, 0) \) 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 \( s_0 \) uncertainty associated with \( \psi(s*, 0) \)
• 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.

Results

<table>
<thead>
<tr>
<th>Location</th>
<th>Study Type</th>
<th>Primary Study VE, BA.1 (95% CI)</th>
<th>Primary Study VE, BA.2 (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>California</td>
<td>Cohen, Delta-dominant</td>
<td>107.55% (2.93), 79.75%</td>
<td>98.48% (3.13), 77.48%</td>
</tr>
<tr>
<td>California</td>
<td>DNA sequencing</td>
<td>107.55% (2.93), 79.75%</td>
<td>98.48% (3.13), 77.48%</td>
</tr>
<tr>
<td>California</td>
<td>SARS-CoV-2</td>
<td>107.55% (2.93), 79.75%</td>
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</tr>
<tr>
<td>Minnesota</td>
<td>DNA sequencing</td>
<td>58.15% (3.58), 72.48%</td>
<td>62.02% (3.96), 77.12%</td>
</tr>
<tr>
<td>Minnesota</td>
<td>SARS-CoV-2</td>
<td>58.15% (3.58), 72.48%</td>
<td>62.02% (3.96), 77.12%</td>
</tr>
<tr>
<td>Rhode Island</td>
<td>DNA sequencing</td>
<td>65.05% (4.15), 80.56%</td>
<td>69.55% (4.67), 84.22%</td>
</tr>
<tr>
<td>Rhode Island</td>
<td>SARS-CoV-2</td>
<td>65.05% (4.15), 80.56%</td>
<td>69.55% (4.67), 84.22%</td>
</tr>
</tbody>
</table>

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.

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