Selecting a Comparison Group for Outcomes Occurring on the Day a Vaccine is Administered

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Background
The 4-valent human papillomavirus (HPV) vaccine (4vHPV vaccine) was licensed for use in males in October 2009 in the US. Hypersensitivity and allergic reactions at the time of vaccination are important safety endpoints for vaccines. In post-marketing observational studies of health outcomes occurring on the day of vaccination, a suitable comparison group is needed to provide context on incidence of outcomes among those vaccinated.

Objective
In an observational safety study, we sought to assess the impact of different comparison groups on measurement of frequency of outcomes occurring on the day of 4vHPV vaccination (Day 0).

Data Source
Optum Research Database (ORD) contains eligibility, pharmacy and medical claims data from a large US health insurer. It is geographically diverse and represents ~4% of the US population.

Methods
Study Population
- Three comparison groups were evaluated:
  1. Comparison Group #1: A matched cohort of males (matched by age and calendar time) with physician office visit for administration of another vaccine (Td/Tdap, meningococcal, or injectable influenza).
  2. Comparison Group #2: A matched cohort of males (matched by age and calendar time) with any health care encounter.
  3. Comparison Group #3: Same patients at a later time point (self-comparison).

Comparison time.
- The number of Gardasil doses differed in Comparison Groups 1 and 2 due to matching criteria and not all initiators in Comparison Group 3 had a self-comparison period.

Outcomes
- Pre-specified events (syncope, epilepsy/convulsions, head trauma, and allergic reactions) were identified with ICD-9 or ICD-10 diagnosis codes.

Analysis
- Outcome frequency was assessed by counts and compared against the 3 comparison groups.

Results
- Comparison Group #1: 160,867 doses matched (79%).
- Comparison Group #2: 202,668 doses matched (~100%).
- Comparison Group #3: 114,035 regimen initiators received at least one dose of 4vHPV (202,737 doses overall). Males may not have contributed self-comparison time.

Table 1. Count of Outpatient, Emergency Room Visit, and Hospitalization Day 0 Outcomes among Regimen Initiators (N=114,035) and Concurrent Controls with Another Vaccine, Concurrent Controls with Health Care Visit, and Post-Vaccination Self-Comparison Period

<table>
<thead>
<tr>
<th>Event Type</th>
<th>Comparison Group #1</th>
<th>Comparison Group #2</th>
<th>Comparison Group #3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outpatient</td>
<td>357</td>
<td>197</td>
<td>393</td>
</tr>
<tr>
<td>Combined</td>
<td>358</td>
<td>201</td>
<td>449</td>
</tr>
<tr>
<td>Hospital/ER</td>
<td>6</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>Combined</td>
<td>101</td>
<td>56</td>
<td>126</td>
</tr>
</tbody>
</table>

Discussion
- Selection of a comparison group for assessment of acute health outcomes on day of vaccination can impact safety conclusions.
- A concurrent control group based on receipt of another vaccine may provide a balanced comparison.
- A concurrent control group not based on receipt of a vaccine but anchored on a healthcare encounter among adolescents may tend to select for those who rarely visit the doctor except for acute health reasons.
- A self-comparison period not anchored on a healthcare encounter for events occurring in a very narrow window (1-day) is unlikely to include a healthcare encounter and may not be a relevant comparison group.

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