WG Interpretation of the EtR Regarding Use of RZV in Immunocompromised Adults, Considerations for Use, and Proposed Policy Options

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CDC Lead, Herpes Zoster Work Group
Policy Question

- Should adults aged ≥19 years who are or will be immunodeficient or immunosuppressed due to disease or therapy be recommended to receive two doses of recombinant zoster vaccine for the prevention of herpes zoster and its complications?

- Including but not limited to:
  1. Hematopoietic stem cell transplant (HSCT) recipients
  2. Patients with hematologic malignancies (HM)
  3. Renal or other solid organ transplant (SOT) recipients
  4. Patients with solid tumor malignancies (STM)
  5. People living with HIV
  6. Patients with primary immunodeficiencies, autoimmune and inflammatory conditions, and taking immunosuppressive medications/therapies
Evidence to Recommendations (EtR) Framework: PICO Question

<table>
<thead>
<tr>
<th><strong>Population</strong></th>
<th>Immunocompromised (IC) adults aged ≥19 years</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intervention</strong></td>
<td>Recombinant zoster vaccine (RZV), 2 doses at least 4 weeks apart*</td>
</tr>
<tr>
<td><strong>Comparison</strong></td>
<td>No vaccine</td>
</tr>
</tbody>
</table>
| **Critical Outcomes** | • Herpes Zoster (HZ)  
• Serious Adverse Events (SAEs) |
| **Important Outcomes** | • Postherpetic Neuralgia (PHN)  
• HZ-Related Hospitalization  
• Immune-Mediated Disease (IMD)  
• Graft versus Host Disease (HSCT)  
• Graft Rejection (SOT)  
• Reactogenicity (Grade 3) |

*First dose at Month 0 followed by a second dose 2 to 6 months later; For individuals who are or will be immunodeficient or immunosuppressed and who would benefit from a shorter vaccination schedule: First dose at Month 0 followed by a second dose 1 to 2 months later.
<table>
<thead>
<tr>
<th>EtR Domain</th>
<th>Question</th>
</tr>
</thead>
<tbody>
<tr>
<td>Public Health Problem</td>
<td>Is the problem of public health importance?</td>
</tr>
<tr>
<td>Benefits and Harms</td>
<td>How substantial are the desirable anticipated effects?</td>
</tr>
<tr>
<td></td>
<td>How substantial are the undesirable anticipated effects?</td>
</tr>
<tr>
<td></td>
<td>Do the desirable effects outweigh the undesirable effects?</td>
</tr>
<tr>
<td>Values</td>
<td>Does the target population feel the desirable effects are</td>
</tr>
<tr>
<td></td>
<td>large relative to the undesirable effects?</td>
</tr>
<tr>
<td></td>
<td>Is there important variability in how patients value the outcomes?</td>
</tr>
<tr>
<td>Acceptability</td>
<td>Is the intervention acceptable to key stakeholders?</td>
</tr>
<tr>
<td>Resource Use</td>
<td>Is the intervention a reasonable and efficient allocation of resources?</td>
</tr>
<tr>
<td>Equity</td>
<td>What would be the impact of the intervention on health equity?</td>
</tr>
<tr>
<td>Feasibility</td>
<td>Is the intervention feasible to implement?</td>
</tr>
</tbody>
</table>
EtR Domain: Public Health Problem
How many IC persons in the United States?

- ~7 million adults with self-reported immunosuppressed status

<table>
<thead>
<tr>
<th>Age Group, y</th>
<th>Prevalence per 100 US Population, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>18-39</td>
<td>1.6 (1.3-1.9)</td>
</tr>
<tr>
<td>40-49</td>
<td>2.3 (1.8-2.8)</td>
</tr>
<tr>
<td>50-59</td>
<td>4.4 (3.7-5.1)</td>
</tr>
<tr>
<td>60-69</td>
<td>3.9 (3.2-4.5)</td>
</tr>
<tr>
<td>70-79</td>
<td>3.1 (2.4-3.8)</td>
</tr>
<tr>
<td>80+</td>
<td>2.5 (1.4-3.5)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>2.7 (2.4-2.9)</strong></td>
</tr>
</tbody>
</table>

Excerpt of Table. Self-reported Immunosuppressed Status.
How many IC persons in the United States?*

- ~3 million among:
  - Hematopoietic stem cell transplant recipients\(^1\)
  - Patients with hematologic malignancies\(^2\)
  - Renal or other solid organ transplant recipients\(^3\)
  - Patients with solid tumor malignancies\(^2,4\)
  - People living with HIV\(^5\)

- ~22 million with autoimmune and/or inflammatory (AI/INF) conditions\(^6\)
  - >80 diverse conditions (e.g., systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease)
  - Often have underlying immune dysfunction, but generally not considered frankly IC unless iatrogenic (i.e., on IC treatments)

Age-specific prevalence highly variable by condition

*References on slide 75
HZ Incidence Common in Adults and Increases with Age

~1 million HZ cases per year in U.S. during pre- HZ vaccine era

2. Figure: CDC, unpublished data; Updated from Harpaz et al. Clinical Infectious Diseases, Volume 69, Issue 2, 15 July 2019, Pages 341–344, https://doi.org/10.1093/cid/ciy953
Public Health Importance
Risk of HZ in IC Groups 1–5

- Median HZ incidence estimates for these IC groups exceeded those reported for immunocompetent adults >50 years


<table>
<thead>
<tr>
<th>Author, year*</th>
<th>Incidence (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bastidas 2019</td>
<td>HCT</td>
</tr>
<tr>
<td>Winston 2018</td>
<td></td>
</tr>
<tr>
<td>Sahoo 2017</td>
<td></td>
</tr>
<tr>
<td>Chen 2014</td>
<td></td>
</tr>
<tr>
<td>Zhang 2017</td>
<td></td>
</tr>
<tr>
<td>Dagnew 2019</td>
<td>HM</td>
</tr>
<tr>
<td>Hebel 2013</td>
<td></td>
</tr>
<tr>
<td>Koo 2013</td>
<td>SOT</td>
</tr>
<tr>
<td>Amass 2008</td>
<td></td>
</tr>
<tr>
<td>Pergam 2011</td>
<td></td>
</tr>
<tr>
<td>Chen 2014</td>
<td></td>
</tr>
<tr>
<td>Tseng 2014</td>
<td>STM</td>
</tr>
<tr>
<td>Mao 2017</td>
<td></td>
</tr>
<tr>
<td>Hebel 2013</td>
<td></td>
</tr>
<tr>
<td>Chen 2014</td>
<td>HIV</td>
</tr>
<tr>
<td>Blank 2012</td>
<td></td>
</tr>
</tbody>
</table>

Figure 3. Herpes zoster incidence rates among patients with selected immunocompromising conditions. *Studies with low or medium risk of bias.
Public Health Importance
Severity of HZ in IC Groups 1–5

- **Postherpetic neuralgia (PHN)**
  - \(\sim6–10\%\) vs \(\sim4\%\) overall in administrative claims databases\(^1\)
  - Between 6% and 45% across IC conditions and studies\(^2\)

- **Disseminated HZ**
  - \(\sim3\%\)\(^2\) of IC, but exceedingly uncommon in healthy persons
  - 10–17% mortality associated with disseminated HZ among renal transplant recipients\(^3,4\)

- **Hospitalization:** 8% of HCT recipients with HZ\(^5\) vs \(<1\%\) of overall Medicare beneficiaries with HZ\(^6\)

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Public Health Importance
Risk of HZ in IC Group 6

- ~2 to 4-fold higher risk in patients with autoimmune conditions than in healthy individuals\(^1\)
- ~1.5-fold higher risk for unvaccinated Medicare beneficiaries with autoimmune conditions vs not IC\(^2\)

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\(^1\)Yun et al. Risk of Herpes Zoster in Autoimmune and Inflammatory Diseases. Arthritis & Rheumatology 2016;68(9):2328-2337.

\(^2\)Izurieta et al. Recombinant Zoster Vaccine (Shingrix) real-world effectiveness in the first two years post-licensure. Clinical Infectious Diseases, 2021;, ciab125, https://doi.org/10.1093/cid/ciab125

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Figure adapted from Yun et al. Bars show the IRs of HZ with 95% confidence intervals. Cohorts of healthy adults without autoimmune diseases or diabetic conditions and adult patients with diabetes were used as controls. SLE=systemic lupus erythematosus; IBD=inflammatory bowel disease; RA=rheumatoid arthritis; PsA=psoriatic arthritis; PsO=psoriasis; AS=ankylosing spondylitis.
Public Health Importance
Risk of HZ in IC Group 6, cont.

- **Age-specific incidence rates among some 21–50-year-olds comparable to or substantially higher than corresponding rates in healthy adults >60 years**

- **Immunosuppressive therapies**
  - ≥1 IC medications = standard of care
  - Not possible to define high risk subgroups based on anticipated therapies
    - Disease modifying anti-rheumatic drugs, or DMARDs (e.g., methotrexate)
    - Glucocorticoids
    - Biologics (e.g., Janus Kinase inhibitors)

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### Incidence Rate (per 1000 person years) of HZ reported in different disease cohorts\(^8\)

<table>
<thead>
<tr>
<th>Age Gp</th>
<th>Healthy</th>
<th>SLE</th>
<th>IBD</th>
<th>RA</th>
<th>PsA</th>
<th>PsO</th>
</tr>
</thead>
<tbody>
<tr>
<td>21–30</td>
<td>2.7</td>
<td>24.6</td>
<td>11.6</td>
<td>6.6</td>
<td>N/A</td>
<td>5.9</td>
</tr>
<tr>
<td>31–40</td>
<td>3.3</td>
<td>15.2</td>
<td>5.6</td>
<td>8.2</td>
<td>9.8</td>
<td>3.7</td>
</tr>
<tr>
<td>41–50</td>
<td>3.9</td>
<td>17.5</td>
<td>10.4</td>
<td>10.0</td>
<td>8.5</td>
<td>6.4</td>
</tr>
<tr>
<td>51–60</td>
<td>5.8</td>
<td>20</td>
<td>11.7</td>
<td>14.6</td>
<td>13.2</td>
<td>9.7</td>
</tr>
<tr>
<td>61–70</td>
<td>8.5</td>
<td>22.7</td>
<td>19.0</td>
<td>17.1</td>
<td>15.9</td>
<td>13.3</td>
</tr>
<tr>
<td>71–85+</td>
<td>10.6</td>
<td>20.9</td>
<td>23.8</td>
<td>21.3</td>
<td>19.4</td>
<td>21.2</td>
</tr>
</tbody>
</table>

*Yun et al.* Risk of Herpes Zoster in Autoimmune and Inflammatory Diseases. Arthritis & Rheumatology 2016;68(9):2328-2337. Excerpt of Table 2. Incidence rate of herpes zoster per 1000 person years by 10 year age group and auto-immune disease or comparator cohort.
Summary

- IC populations are very heterogeneous, both across and within groups and among individuals over time.
- Risk of HZ and HZ complications generally higher in IC populations, although there is variability across and within IC groups.
- Not feasible to define every possible IC condition, medication/therapy combination.
- Important to consider broad recommendations and provider guidance for IC populations.
Is herpes zoster in immunocompromised adults of public health importance?

- No
- Probably no
- Probably yes
- Yes
- Varies
- Don't know
EtR Domain: Benefits and Harms
## Systematic Review

### Information Sources

- Medline
- Embase
- CINAHL
- Cochrane
- Scopus
- clinicaltrials.gov
- Potentially obtain unpublished and other relevant data by hand-searching reference lists, and consulting with vaccine manufacturers and subject matter experts.

### Inclusion and Exclusion Criteria

**Inclusion criteria**

- Provide data on vaccination with RZV
- Involve human subjects
- Include immunocompromised adults
- Any language
- Date based on earliest RZV article (estimated ~2012 with RZV phase I/II trial article by Leroux-Roels et al.)

**Exclusion criteria**

- Animal studies

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### Additional criteria for GRADE review

- Restricted to PICO-defined population, intervention, comparison, and outcomes
  - Comparison group available for outcomes of interest (and not modeled or historical)
  - For benefits: at least 2 doses of RZV; for harms: at least 1 dose of RZV
  - Vaccine components included in current RZV vaccine (i.e., AS01B adjuvant)
COVIDENCE Review PRISMA Diagram

Studies imported for screening (n = 2406) → Records screened (n = 2396) → Records assessed for eligibility (n = 133) → Full-text articles excluded (n = 114)

- 53 duplicate or results published in another manuscript
- 22 wrong patient population
- 14 wrong intervention
- 13 abstract only
- 12 study ongoing

Records published after initial data cutoff (4/2021) (n = 2) → Duplicates removed (n=12)

- Abstracts & titles removed (n = 2263)
### Appendix 1. Studies Included in the Review of Evidence

<table>
<thead>
<tr>
<th>Study</th>
<th>Study design</th>
<th>Country</th>
<th>Study Population, Age</th>
<th>N Intervention</th>
<th>N comparison</th>
<th>Outcomes</th>
<th>Funding</th>
</tr>
</thead>
</table>
| Bastidas, 2019       | Phase III RCT                 | Multiple countries, including US             | Autologous HSCT recipients ≥18 years                                                   | 1 dose: 922     | 1 dose: 924   | • Confirmed HZ, PHN & HZ-Related Hospitalizations  
  • Immunogenicity  
  • Reactogenicity  
  • SAEs, pIMDs                                         | GSK     |
| Berkowitz, 2015      | Phase I/II RCT                | Multiple countries, including US             | Patients with HIV ≥18 years                                                              | 1 dose: 74      | 1 dose: 49    | • Confirmed HZ  
  • Immunogenicity  
  • Reactogenicity  
  • SAEs                                         | GSK     |
| Dagnew, 2019         | Phase III RCT                 | Multiple countries, including US             | Patients with hematological malignancy ≥18 years                                        | 1 dose: 283     | 1 dose: 279   | • Confirmed HZ  
  • Immunogenicity  
  • Reactogenicity  
  • SAEs                                         | GSK     |
| Dagnew, 2021         | Pooled post hoc analysis of two Phase III RCTs | Multiple countries, including US             | Participants with pIMDs not on immune-suppressive therapies ≥50 years; ≥70 years        | 1 dose: 983     | 1 dose: 960   | • Post hoc efficacy of RZV in preventing HZ  
  • SAEs, pIMDs                                         | GSK     |
| Stadtmauer, 2014     | Phase I/II RCT                | United States                                | Autologous HSCT recipients ≥18 years                                                    | 3 doses: 30     | 3 doses: 30   | • Confirmed HZ  
  • Immunogenicity  
  • Reactogenicity  
  • SAEs, pIMDs                                         | GSK     |
| Vink, 2019           | Phase II/III RCT              | Canada, Czech Republic, France, Korea, Spain | Solid tumor patients ≥18 years                                                           | 1 dose: 117     | 1 dose: 115   | • Immunogenicity  
  • Reactogenicity  
  • SAEs, pIMDs                                         | GSK     |
| Vink, 2020           | Phase III RCT                 | Belgium, Canada, Finland, Taiwan, Spain,     | Renal transplant patients ≥18 years receiving daily immunosuppressive therapy          | 1 dose: 132     | 1 dose: 132   | • Immunogenicity  
  • Reactogenicity  
  • SAEs, pIMDs (including graft rejection, pIMDs) | GSK     |
| Izurieta, 2021       | Cohort Study                  | United States                                | Medicare beneficiaries ≥65 years with IC or AI conditions                                | 1 dose: 92,069  | 1 dose: 86,123 | • Vaccine efficacy of RZV in preventing HZ (stratified by IC and AI conditions)             | US FDA, CMS |
| Khan, 2021           | Cohort Study                  | United States                                | Patients with IBD ≥50 years in the Veterans Affairs Healthcare System                    | 50–60: 655     | 50–60: 5,995  | • Vaccine efficacy of RZV in preventing HZ (stratified by age and steroid use)              | Pfizer  |

**Abbreviations:** AI = Autoimmune; CMS = Center for Medicare and Medicaid Services; FDA = Food and Drug Administration; GSK = GlaxoSmithKline; HSCT = Hematopoietic Stem Cell Transplant; HZ = Herpes Zoster; IBD = Inflammatory Bowel Disease; IC = Immunocompromised; pIMDs = Potential Immune-Mediated Disease; RCT = Randomized Control Trial; RZV = Recombinant Zoster Vaccine; SAEs = Serious Adverse Events
### Outcomes for GRADE

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Importance</th>
<th>Design (# of studies)</th>
<th>Findings</th>
<th>Evidence Type</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Benefits</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Herpes Zoster (HZ)</td>
<td>Critical</td>
<td>RCT(5) OBS(2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Postherpetic Neuralgia (PHN)</td>
<td>Important</td>
<td>RCT(1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HZ-Related Hospitalization</td>
<td>Important</td>
<td>RCT(1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Harms</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serious adverse events (SAE)</td>
<td>Critical</td>
<td>RCT(7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Immune-Mediated Disease</td>
<td>Important</td>
<td>RCT(6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Graft vs. Host Disease (HCT)</td>
<td>Important</td>
<td>RCT(1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Graft Rejection (SOT)</td>
<td>Important</td>
<td>RCT(1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reactogenicity (Grade 3)</td>
<td>Important</td>
<td>RCT(6)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Evidence type: 1=high; 2=moderate; 3=low; 4=very low; ND, no data
# Outcome 1: Herpes Zoster (HZ)
## Randomized Studies with Unvaccinated Comparator (n=5)

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Events/Vaccine (n/N)</th>
<th>Events/Placebo (n/N)</th>
<th>VE</th>
<th>95% CI</th>
<th>Study Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bastidas ’19</td>
<td>Autologous HSCT recipients ≥18</td>
<td>49/870 (5.6%)</td>
<td>135/851 (15.9%)</td>
<td>68.2%</td>
<td>55.6 % -77.5%</td>
<td>Not serious</td>
</tr>
<tr>
<td></td>
<td>• 18-49 subset</td>
<td>9/213 (4.2%)</td>
<td>29/212 (13.7%)</td>
<td>72%</td>
<td>39% - 88%*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• ≥50 subset</td>
<td>40/657 (6.1%)</td>
<td>106/639 (16.6%)</td>
<td>67%</td>
<td>53% - 78%*</td>
<td></td>
</tr>
<tr>
<td>Berkowitz ’15</td>
<td>Patients with HIV ≥18</td>
<td>0/72 (0.0%)</td>
<td>0/47 (0.0%)</td>
<td>NE</td>
<td>NE</td>
<td>Not serious</td>
</tr>
<tr>
<td>Dagnew ’19</td>
<td>Hematological malignancy ≥18</td>
<td>2/259 (0.77%)</td>
<td>14/256 (5.47%)</td>
<td>87.2%</td>
<td>44.3% - 98.6%</td>
<td>Not serious</td>
</tr>
<tr>
<td>Dagnew ’21</td>
<td>pIMDs ≥50; ≥70</td>
<td>4/936 (0.43%)</td>
<td>38/923 (4.12%)</td>
<td>90.5%</td>
<td>73.5% - 97.5%</td>
<td>Serious**</td>
</tr>
<tr>
<td></td>
<td>• 50-59 subset</td>
<td>1/222 (0.45%)</td>
<td>11/201 (5.47%)</td>
<td>92.8%</td>
<td>50.5% - 99.8%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• 60-69 subset</td>
<td>0/159 (0.0%)</td>
<td>8/151 (5.30%)</td>
<td>100%</td>
<td>54.9% - 100%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• 70-79 subset</td>
<td>2/427 (0.47%)</td>
<td>13/450 (2.89%)</td>
<td>84.4%</td>
<td>30.8% - 98.3%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• ≥80 subset</td>
<td>1/128 (0.78%)</td>
<td>6/121 (4.96%)</td>
<td>86.2%</td>
<td>-13.5% - 99.7%</td>
<td></td>
</tr>
<tr>
<td>Stadtmauer ‘14</td>
<td>Autologous HCT recipients ≥18</td>
<td>0/61 (0%)</td>
<td>2/30 (6.67%)</td>
<td>RR: 0.0</td>
<td>0-NA***</td>
<td>Not serious</td>
</tr>
</tbody>
</table>

* Incidence Rate Ratios (IRRs) were presented rather than VE, and VE was calculated using the formula VE = (100 * (1-IRR)).
** While the RCTs met low risk of bias criteria, given this analysis for this subgroup was post hoc and the analysis was not powered for this outcome nor able to address type 1 error, this analysis has moderate/high risk of bias.
*** RR and Wald confidence intervals calculated in R and in SAS.
Outcome 1: Herpes Zoster (HZ)
Observational Studies with Unvaccinated Comparator (n=2)

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Population</th>
<th>n/N (Vaccinated)</th>
<th>n/n (Unvaccinated)</th>
<th>VE (%) (95% CI)</th>
<th>Study Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Izurieta, 2021</td>
<td>Prospective cohort</td>
<td>Medicare patients ≥65</td>
<td>167/61,999 (0.27%)</td>
<td>20,640/886,123 (2.33%)</td>
<td>68.0% (62.3% - 72.8%)</td>
<td>Serious*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Autoimmune condition</td>
<td>143/40,442 (0.35%)</td>
<td>18,504/746,654 (2.48%)</td>
<td>64.1% (57.2% - 69.8%)</td>
<td></td>
</tr>
<tr>
<td>Khan, 2021</td>
<td>Retrospective cohort</td>
<td>VAHS patients with IBD ≥50</td>
<td>8/4,875 (0.16%)</td>
<td>337/26,549 (1.27%)</td>
<td>Hazard Ratios reported below**</td>
<td>Serious ***</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• 50-60 subset</td>
<td>0/655 (0.0%)</td>
<td>69/5,995 (1.15%)</td>
<td>• No steroid use: NE</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• &gt;60 subset</td>
<td>8/4,220 (0.19%)</td>
<td>268/20,554 (1.30%)</td>
<td>• Steroid use: 0.41 (0.19-0.87)</td>
<td></td>
</tr>
</tbody>
</table>

* This study presents with concerns with confounding, with no demographics or risk-factors presented for the immune-compromised and autoimmune populations. Additionally, it is a Medicare claims study, reliant on algorithmic determination of immunocompromised and autoimmune status, thus there is significant risk of confounding and information bias in interpreting the VE.

**Khan 2021 reported results of a Cox regression model (HR) without any interaction and found that full dose of RZV was associated with lower risk of HZ compared with the unvaccinated group, after adjusting for other baseline and time-varying covariates. Specifically, in the 50 to 60-year-old group, the HR was 0 (95% CI, 0.0;P<.001). The HR was 0.39 (95% CI,0.19-0.80;P=.01) in the >60-year-old group. The HRs for steroid and non-steroid users are presented in the table above.

***This was a large cohort analysis, yet the VA patient population may not be generalizable to the general population (e.g., study population was heavily skewed male). Coupled with the authors' retrospective case ascertainment, we would consider this analysis moderate/high risk of bias.
### Outcome 1: HZ – Immunogenicity as Surrogate
#### Randomized Studies with Unvaccinated Comparator (n=6)

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Timing after last dose</th>
<th>Humoral Immunity</th>
<th>Cell-mediated Immunity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>% Response Rate</td>
<td>% Response Rate</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>RZV (95% CI)</td>
<td>Placebo (95% CI)</td>
</tr>
<tr>
<td>Bastidas, 2019</td>
<td>Autologous HSCT patients ≥18</td>
<td>1 Month</td>
<td>67% (87-99.5%)</td>
<td>0%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>12 Months</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Berkowitz, 2015</td>
<td>Patients with HIV ≥18*</td>
<td>1 Month</td>
<td>96.2% (87-99.5%)</td>
<td>2.8% (0.1-14.5%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>12 Months</td>
<td>91.7% (80-97.7%)</td>
<td>0% (0-9.5%)</td>
</tr>
<tr>
<td>Dagnew, 2019</td>
<td>Patients with hematological malignancy ≥18</td>
<td>1 Month</td>
<td>65.4% (58.7-71.7%)</td>
<td>0.5% (0.0-2.8%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>12 Months</td>
<td>52.1% (44.2-59.9%)</td>
<td>3.6% (1.2-8.1%)</td>
</tr>
<tr>
<td>Stadtmauer, 2014</td>
<td>Autologous HCT recipients ≥18</td>
<td>1 Month</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>12 Months</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Vink, 2019</td>
<td>Solid Tumor Patients ≥18</td>
<td>1 Month</td>
<td>86.2%</td>
<td>0.0%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>12 Months</td>
<td>51.5%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Vink, 2020</td>
<td>Renal transplant patients ≥18</td>
<td>1 Month</td>
<td>80.2%</td>
<td>4.2%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>12 Months</td>
<td>66.7%</td>
<td>6.4%</td>
</tr>
</tbody>
</table>

* Berkowitz et al. evaluated a 3-dose regimen of RZV, thus immunogenicity results are presented 1 and 12 months after the 3rd dose was received. Stadtmauer evaluated both a 2- and 3-dose regimen. Results are presented for the 2-dose regimen in the table. 3-dose results can be found in the Appendix.

** CMI GMR: 9.94 (95% CI, 3.63-27.19)

*** CMI GMR: 17.26 (5.92-50.36)

All studies had low risk of bias/no major study limitations.
### Outcome 1 Evidence Table: Herpes Zoster

<table>
<thead>
<tr>
<th>Certainty Assessment</th>
<th>Number of Patients (%)</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prevent Herpes Zoster (HZ)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RCT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>#</td>
<td>Study Design</td>
<td>Risk of Bias</td>
</tr>
<tr>
<td>5</td>
<td>RCT</td>
<td>not serious</td>
</tr>
<tr>
<td>6</td>
<td>RCT – Immunogenicity</td>
<td>not serious</td>
</tr>
<tr>
<td>2</td>
<td>Cohort</td>
<td>not serious</td>
</tr>
</tbody>
</table>

*All immunogenicity metrics presented at 1 month after last dose.

**The RCTs cover a wide range of populations that cover some, but not all the populations being considered for the recommendation. Assessing them together results in a downgrade (-1) for indirectness.

***Interpreting immunogenicity results for prevention of HZ faces a very serious (-2) downgrade for indirectness due to indirectness in two domains of the PICO question: population, and outcome. For population, the included studies evaluate the immunogenicity of RZV in some, but not all the populations considered for the recommendation. Additionally, there is inconsistency in using the proxy measure of immunogenicity to evaluate vaccine efficacy, or prevention of HZ, given that there are no established correlates of protection.

****The cohort studies assessed incidence of HZ in autoimmune/immunocompromised patients enrolled in Medicare, and IBD patients in the VA, which do not represent all populations under consideration for the recommendation.
Outcome 4: SAEs
Randomized Studies with Unvaccinated Comparator (n=7)

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>SAE/Vaccine (n/N)</th>
<th>SAE/Placebo (n/N)</th>
<th>SAE/Vaccine (n/N) related to vaccination</th>
<th>SAE/Placebo (n/N) related to vaccination</th>
<th>RR (95% CI)**</th>
<th>Study Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bastidas, 2019</td>
<td>Autologous HSCT patients ≥18</td>
<td>263/922 (28.5%)</td>
<td>241/924 (26.1%)</td>
<td>3/922 (0.33%)</td>
<td>4/924 (0.43%)</td>
<td>1.09 (0.94, 1.27)</td>
<td>Not serious</td>
</tr>
<tr>
<td>Berkowitz, 2015</td>
<td>Patients with HIV ≥18</td>
<td>6/74 (8.1%)</td>
<td>2/49 (4.1%)</td>
<td>0/74 (0.0%)</td>
<td>0/49 (0.0%)</td>
<td>1.99 (0.42, 9.44)</td>
<td>Not serious</td>
</tr>
<tr>
<td>Dagnew, 2019</td>
<td>Patients with hematologic malignancy ≥18</td>
<td>66/283 (23.3%)</td>
<td>82/279 (29.4%)</td>
<td>1/283 (0.35%)</td>
<td>1/279 (0.36%)</td>
<td>0.79 (0.60, 1.05)</td>
<td>Not serious</td>
</tr>
<tr>
<td>Dagnew, 2021</td>
<td>Patients with pIMDs ≥50; ≥70</td>
<td>144/983 (14.6%)</td>
<td>112/960 (11.7%)</td>
<td>not disclosed</td>
<td>not disclosed</td>
<td>1.26 (1.00, 1.58)</td>
<td>Serious***</td>
</tr>
<tr>
<td>Stadtmauer, 2014</td>
<td>Autologous HSCT recipients ≥18</td>
<td>16/61 (26.2%)*</td>
<td>8/30 (26.7%)</td>
<td>1/61 (1.6%)</td>
<td>0/30 (0.0%)</td>
<td>0.98 (0.48, 2.04)</td>
<td>Not serious</td>
</tr>
<tr>
<td>Vink, 2019</td>
<td>Solid tumor patients ≥18</td>
<td>46/117 (39.3%)</td>
<td>45/115 (39.1%)</td>
<td>0/117 (0.0%)</td>
<td>0/115 (0.0%)</td>
<td>1.00 (0.73, 1.38)</td>
<td>Not serious</td>
</tr>
<tr>
<td>Vink, 2020</td>
<td>Renal transplant patients ≥18</td>
<td>26/132 (19.7%)</td>
<td>33/132 (25.0%)</td>
<td>0/132 (0.0%)</td>
<td>1/132 (0.76%)</td>
<td>0.79 (0.50, 1.24)</td>
<td>Not serious</td>
</tr>
</tbody>
</table>

*These SAEs reflect 6 in the 3-dose gE/AS01B gp: (6/30, 20.0%), and 10 in the 2-dose gp: 10/31 (32.3%). Of those, only 1 was related to vaccination in the 2-dose gp: 1/31 (3.23%).

**RRs were calculated using Wald confidence intervals in R and SAS.

***While the RCTs (ZOE 50/70) met low risk of bias criteria, given this analysis for this subgroup was post hoc and the analysis was not powered for this outcome nor able to address type 1 error, this analysis has moderate/high risk of bias.
Outcome 4 Evidence Table: SAEs

*Across the 7 included RCTs (one of which was a pooled post-hoc analysis of two RCTs (ZOE-50 and ZOE-70), among a subset of participants who reported at least one pIMD at enrollment), there are a wide range of populations included: Autologous HSCT patients (Bastidas, Stadtmauer), patients with HIV (Berkowitz), patients with hematologic malignancies (Dagnew 2019), patients with pIMDs (Dagnew 2021), patients with solid tumors receiving cytotoxic or immunosuppressive therapy (Vink 2019), and renal transplant patients on daily immunosuppression (Vink 2020). The wide variety of patient sub-populations being pooled together for this analysis results in a downgrade for indirectness (-1).

<table>
<thead>
<tr>
<th>No of studies</th>
<th>Study design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other</th>
<th>RZV</th>
<th>Comparison</th>
<th>Effect</th>
<th>Certainty</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>RCT</td>
<td>not serious</td>
<td>not serious</td>
<td>serious*</td>
<td>not serious</td>
<td>none</td>
<td>SAEs ranged from 8.1% to 39.3%</td>
<td>SAEs ranged from 4.1% to 39.1%</td>
<td>RR ranged from 0.79 (0.60, 1.05) to 1.99 (0.42, 9.44), with 3 studies reporting RR &lt;1, 3 studies reporting RR &gt;1, and one reporting RR = 1</td>
<td>Type 2 Moderate</td>
<td>CRITICAL</td>
</tr>
</tbody>
</table>
## Summary of GRADE

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Importance</th>
<th>Design (# of studies)</th>
<th>Findings</th>
<th>Evidence Type</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Benefits</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Herpes Zoster (HZ)</td>
<td>Critical</td>
<td>RCT(5) OBS(2)</td>
<td>VE ranged from 68.2% to 87.2% for those 18+, and VE was 90.5% for those over 50 with pIMDs not on immunosuppressants. Observational studies showed VE of 64.1% among IC populations, 68.0% among AI populations.</td>
<td>Type 2</td>
</tr>
<tr>
<td>Postherpetic Neuralgia (PHN)</td>
<td>Important</td>
<td>RCT(1)</td>
<td>VE of 89% (12%-100%)</td>
<td>Type 3</td>
</tr>
<tr>
<td>HZ-Related Hospitalization</td>
<td>Important</td>
<td>RCT(1)</td>
<td>VE of 85% (32%-97%)</td>
<td>Type 3</td>
</tr>
<tr>
<td><strong>Harms</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serious adverse events (SAE)</td>
<td>Critical</td>
<td>RCT(7)</td>
<td>Not increased in RZV group: SAEs were common in both vaccine and placebo groups, with RR ranging from 0.79 to 1.99 and all confidence intervals including null effect. SAEs attributed to vaccination were rare.</td>
<td>Type 2</td>
</tr>
<tr>
<td>- Immune-Mediated Disease</td>
<td>Important</td>
<td>RCT(6)</td>
<td>Not increased in RZV group: RRs ranged from 0.68 to 2.0 but confidence intervals included null effect.</td>
<td>Type 4</td>
</tr>
<tr>
<td>- Graft vs. Host Disease (HSCT)</td>
<td>Important</td>
<td>RCT(1)</td>
<td>Not increased in RZV group: RR of 0.83 (0.21, 3.24)</td>
<td>Type 4</td>
</tr>
<tr>
<td>- Graft Rejection (SOT)</td>
<td>Important</td>
<td>RCT(1)</td>
<td>Not increased in RZV group: RR of 0.57 (0.17, 1.91)</td>
<td>Type 3</td>
</tr>
<tr>
<td>Reactogenicity (Grade 3)</td>
<td>Important</td>
<td>RCT(6)</td>
<td>Increased in RZV group: The vaccine is reactogenic, with RRs ranging from 1.19 to 2.49 for systemic symptoms, and RR=42 for local symptoms.</td>
<td>Type 2</td>
</tr>
</tbody>
</table>
Benefits and Harms:
Work Group Interpretation

How substantial are the desirable anticipated effects of RZV in IC adults?

- Minimal
- Small
- Moderate
- Large
- Varies
- Don't know
Benefits and Harms:
Work Group Interpretation

How substantial are the undesirable anticipated effects of RZV in IC adults?

- Minimal
- Small
- Moderate
- Large
- Varies
- Don't know
Benefits and Harms: Work Group Interpretation

Do the desirable effects outweigh the undesirable effects?

- Favors intervention (RZV, 2 doses at least 4 weeks apart)
- Favors comparison (no vaccine)
- Favors both
- Favors neither
- Unclear
EtR Domain: Values
Values

- Limited data on knowledge, attitudes, and practices (KAP) among IC patients regarding potential use of RZV for prevention of HZ and its complications

- In general
  - Zoster vaccination (including zoster vaccine live, or ZVL, and RZV) is increasing (from 6.7% in 2008 to 34.5% in 2018,\(^1\) to 41.2% in 2019\(^2\))
  - RZV series completion rates are high
    - Among Medicare enrollees from 2016–2019, 67% received 2 RZV doses\(^3\)
    - 70% completion after 6 months, 80% completion after 12 months (IQVIA data)\(^4\)

Although there is no ACIP recommendation, IC patients recognize the increased risk of HZ and many have already received RZV*.

Concerns related to Grade 3 reactions may discourage some IC patients from getting RZV.

Summary

- IC patients desire the ability to receive RZV to prevent HZ and its complications
- Many IC patients already pursuing vaccination with RZV
- The ACIP HZWG placed high value on prevention of HZ and its complications in IC adults
- Given the burden of HZ and its complications in these patients, it is anticipated that more IC patients would pursue vaccination with RZV if recommended by ACIP and their provider
<table>
<thead>
<tr>
<th>Values:</th>
<th>Work Group Interpretation</th>
</tr>
</thead>
</table>

Does the target population feel that the desirable effects of RZV are large relative to undesirable effects?

- No
- Probably no
- **Probably yes**
- Yes
- Varies
- Don't know
Is there important uncertainty about, or variability in, how much people value the main outcomes?

- Important uncertainty or variability
- Probably important uncertainty or variability
- **Probably not important uncertainty or variability**
- No important uncertainty or variability
- No known undesirable outcomes
EtR Domain: Acceptability
Primary Care Physicians’ Perspective Related to Recombinant Zoster Vaccine, 2020*

- **Objectives:** To assess among primary care physicians serving adults regarding RZV
  - Current practices, attitudes, knowledge, barriers to recommending
  - Likelihood of recommending to IC among physicians who had not recommended to IC patients

- **Methods**
  - Surveyed physicians in existing Vaccine Policy Collaborative Initiative (VPCI) sentinel networks
  - Family Physician (FP) and General Internist (GIM) results combined with any differences highlighted

*Hurley et al., unpublished data
Physician Strength of Recommendation for RZV in Different Types of Patients, United States, 2020

Recommendations Consistent with ACIP Recommendations

- Healthy adults ≥ 50 years old (n = 599):
  - Strongly recommend OR recommend, but not strongly: 96%
  - Don't recommend for or against: 4%

- Adults ≥ 50 years old anticipating having a bone marrow or solid organ transplant who are not yet on immunosuppressive therapy (n=547):
  - Strongly recommend OR recommend, but not strongly: 79%
  - Don't recommend for or against: 3%

- Adults ≥ 50 years old on low dose methotrexate (<0.4mg/kg) (n=581):
  - Strongly recommend OR recommend, but not strongly: 70%
  - Don't recommend for or against: 6%

*Hurley et al., unpublished data
Physician Strength of Recommendation for RZV in Different Types of Patients, United States, 2020 (n=632)

**Recommendations Among Populations without an ACIP recommendation**

- **Adults ≥ 50 years old with HIV (CD4 count >200)** (n=494)
  - Strongly recommend OR recommend, but not strongly: 67%
  - Don’t recommend for or against: 4%
  - Recommend against: 27%

- **Adults ≥ 50 years old on a recombinant human immune mediator or immune modulator (e.g. Remicade)** (n=579)
  - Strongly recommend OR recommend, but not strongly: 56%
  - Don’t recommend for or against: 7%
  - Recommend against: 4%
  - Defer to subspecialist: 34%

- **Adults ≥ 50 years old on chemotherapy** (n=584)
  - Strongly recommend OR recommend, but not strongly: 48%
  - Don’t recommend for or against: 6%
  - Recommend against: 6%
  - Defer to subspecialist: 40%

- **Adults ≥ 50 years old receiving immunosuppressive therapy for a bone marrow or solid organ transplant** (n=543)
  - Strongly recommend OR recommend, but not strongly: 42%
  - Don’t recommend for or against: 7%
  - Recommend against: 9%
  - Defer to subspecialist: 42%

- **Adults 18-49 years old with an immunocompromising condition** (n=583)
  - Strongly recommend OR recommend, but not strongly: 31%
  - Don’t recommend for or against: 36%
  - Recommend against: 18%
  - Defer to subspecialist: 14%

- **Healthy adults 18-49 years old** (n=596)
  - Strongly recommend OR recommend, but not strongly: 4%
  - Don’t recommend for or against: 45%
  - Recommend against: 51%

* 45% GIM vs. 38% FP ‘Strong Recommend,’ p<0.05

*Hurley et al., unpublished data
Likelihood of Recommending RZV to Different Types of IC Patients Among Physicians Who Had Not Recommended RZV to IC Patients*

<table>
<thead>
<tr>
<th>Demographic</th>
<th>Very Likely</th>
<th>Somewhat Likely</th>
<th>Somewhat Unlikely</th>
<th>Very Unlikely</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults 18-49 years with HIV (CD4 count &gt;200) (n=295)</td>
<td>48%</td>
<td>28%</td>
<td>8%</td>
<td>16%</td>
</tr>
<tr>
<td>Adults 18-49 years on a recombinant human immune mediator or immune modulator (e.g. Remicade) (n=333)</td>
<td>41%</td>
<td>31%</td>
<td>12%</td>
<td>15%</td>
</tr>
<tr>
<td>Adults 18-49 years receiving immunosuppressive therapy for a bone marrow or solid organ transplant (n=308)</td>
<td>41%</td>
<td>29%</td>
<td>11%</td>
<td>20%</td>
</tr>
<tr>
<td>Adults ≥ 50 years with HIV (CD4 count &gt;200) (n=112)</td>
<td>43%</td>
<td>33%</td>
<td>9%</td>
<td>15%</td>
</tr>
<tr>
<td>Adults ≥ 50 years on a recombinant human immune mediator or immune modulator (e.g. Remicade) (n=208)</td>
<td>40%</td>
<td>33%</td>
<td>13%</td>
<td>15%</td>
</tr>
<tr>
<td>Adults ≥ 50 years receiving immunosuppressive therapy for a bone marrow or solid organ transplant (n=247)</td>
<td>46%</td>
<td>23%</td>
<td>14%</td>
<td>17%</td>
</tr>
</tbody>
</table>

*Some percentages do not add up to 100% due to rounding

*Hurley et al., unpublished data
Summary

- Given highly specialized care and increased HZ risk among IC patients, work group noted vaccination is favored if there are no safety concerns
  - Although currently available evidence considered acceptable, additional safety data is a research need

- Despite lack of a recommendation from ACIP, many physicians are recommending RZV to patients with IC conditions
  - Physicians need more direction on which patients are eligible for RZV
  - Substantial minority would be unlikely to recommend RZV to various IC patients even if it were licensed, recommended and covered by insurance for them (without input from a subspecialist)

- Many specialty organizations recommending RZV for IC adults

- Anticipate would increase with FDA approval and ACIP recommendation
Acceptability:
Work Group Interpretation

Is RZV in IC adults acceptable to key stakeholders?

- No
- Probably no
- Probably yes
- Yes
- Varies
- Don't know
EtR Domain: Resource Use
Cost-Effectiveness Assessments

<table>
<thead>
<tr>
<th>Scenario</th>
<th>GSK</th>
<th>CDC</th>
</tr>
</thead>
<tbody>
<tr>
<td>HSCT (Base case)</td>
<td>Cost-saving, $140*</td>
<td>Cost-saving</td>
</tr>
<tr>
<td>Multiple Myeloma</td>
<td>n/r</td>
<td>Cost-saving</td>
</tr>
<tr>
<td>Renal transplant</td>
<td>Cost-saving</td>
<td>n/r</td>
</tr>
<tr>
<td>Hematologic malignancy</td>
<td>n/r</td>
<td>$10,000</td>
</tr>
<tr>
<td>HIV</td>
<td>$33,000</td>
<td>$79,000</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>$68,000</td>
<td>n/r</td>
</tr>
<tr>
<td>Hodgkin lymphoma</td>
<td>$96,000</td>
<td>n/r</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>n/r</td>
<td>$99,000</td>
</tr>
<tr>
<td>Autoimmune &amp; inflammatory</td>
<td>150,000**</td>
<td>$208,000</td>
</tr>
</tbody>
</table>

*Cost-savings from societal perspective, $140 from healthcare perspective. n/r = not reported.

**Implicit AI/INF scenario: Assuming starting age 25 years, HZ incidence 10/1000PY and duration of IC status 5 years.

Ortega-Sanchez. Economics of vaccinating immunocompromised 19–49-year-old adults against herpes zoster in the US. September 2021 ACIP Meeting. Available at: https://www.cdc.gov/vaccines/acip/meetings/slides-2021-09-29.html.
Summary

- **Base-case: HSCT patients**
  - Economic value of RZV appears to be *favorable* (i.e., cost-saving)
  - Higher HZ incidence and HZ-related health care costs, and reasonable VE
  - Smaller patient population

- **Scenarios: Other patient groups (e.g., HIV, AI/INF)**
  - With lower risk of HZ, severe outcomes, and lower health care costs, the economic value of RZV vaccination was less favorable relative to HSCT patients
  - Some AI/INF conditions may have *the least favorable* estimates of RZV use, depending on the underlying risk of HZ
  - Larger patient population for AI/INF
Summary

- Considering results across the base case and scenarios from both models, the ACIP HZWG determined the estimated economic values to be generally favorable.

- Given highly specialized care and resources invested for base-case and other IC populations, the work group did not consider cost-effectiveness assessments to be a main driver for decision-making.
Resource Use:
Work Group Interpretation

Is RZV in IC adults a reasonable and efficient allocation of resources?

○ No  ○ Probably no  ○ Probably yes  ○ Yes  ○ Varies  ○ Don't know
EtR Domain: Equity
What Would be the Impact of the Intervention on Health Equity?

- **2018 NHIS data**
  - Overall, HZ vaccination coverage among adults aged ≥50 and ≥60 years was 24.1% and 34.5%, respectively
  - White adults aged ≥50 and ≥60 years had higher coverage (28.0% and 38.6%, respectively) compared with Blacks (12.4% and 18.8%, respectively), Hispanics (12.2% and 19.5%, respectively), and Asians (19.6% and 29.1%, respectively)

- **2010–2019 NHIS data**
  - In general, race/ethnicity, household income, education level, and health insurance type significantly associated with receipt of zoster vaccinations among adults aged ≥65 years

---

Summary

- Anticipate ACIP recommendation would increase access overall since
  - Increases scope of population eligible to be vaccinated
  - Ensures coverage under ACA

- However, will likely still be challenges with uptake given
  - Previously noted race/ethnicity, household income, education level, and insurance disparities
  - Variability in health insurance coverage and lack of insurance, which may result in out-of-pocket costs for some patients

- Important to continue monitoring RZV vaccination through the NHIS, including stratifying by health status and race/ethnicity

- Work group also noted that equity could potentially be monitored at the local level during implementation
Equity:
Work Group Interpretation

What would be the impact of RZV in IC adults on health equity?

- Reduced
- Probably reduced
- Probably no impact
- Probably increased
- Increased
- Varies
- Don't know
EtR Domain: Feasibility
Is the Intervention Feasible to Implement?

- RZV is a refrigerator-stable, two-dose vaccine
- Can be co-administered with other adult vaccinations
- U.S. health care system has experience delivering RZV to immunocompetent adults aged ≥50 years
- Various systemic factors challenge the adult vaccination program in the U.S.
Physicians from smaller (median: 5 providers) and private practices were less likely to stock RZV than larger practices or HMO or hospital-based clinics (p=<0.001).

*Hurley et al., unpublished data
Do you refer patients to receive SHINGRIX at a location outside of your practice? (n=616)

If yes, how often do you refer to the following locations? (n= 538)

*Hurley et al., unpublished data
Role of Pharmacies

- Already a major provider of RZV, with ~60–65% of RZV distributed to/administered in pharmacies

- Anticipated concerns in the pharmacy setting
  - Identification of IC patients (e.g., based on immunosuppressive medications, self-reported immunosuppression)
  - Standing orders
  - Some pharmacies may be out of network, which could result in out-of-pocket costs for patients
Identification of IC Patients may be Challenging

- **Highlights need for**
  - Provider and patient education materials
  - Clinical decision support

- **Majority of Jurisdictions have lifelong Immunization Information Systems (IISs)**
  - Can receive adult immunization information
  - Many do not receive health status information, therefore anticipate will increase reliance on other systems (e.g., EHRs) for decision support

- **Work group noted that clinical decision support guidance would be helpful and that it will be important to**
  - Promote best practices*
  - Encourage providers to upload and update RZV vaccination information in Jurisdiction IISs

*Resources available at Immunization Information Systems (IIS) | CDC
Feasibility: Work Group Interpretation

Is RZV in IC adults feasible to implement?

○ No  ○ Probably no  ○ Probably yes  ○ Yes  ○ Varies  ○ Don't know
EtR Summary
<table>
<thead>
<tr>
<th>EtR Domain</th>
<th>Question</th>
<th>Work Group Judgments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Public Health</td>
<td>Is the problem of public health importance?</td>
<td>Yes</td>
</tr>
<tr>
<td>Problem</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benefits and</td>
<td>How substantial are the desirable anticipated effects?</td>
<td>Large</td>
</tr>
<tr>
<td>Harms</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>How substantial are the undesirable anticipated effects?</td>
<td>Small</td>
</tr>
<tr>
<td></td>
<td>Do the desirable effects outweigh the undesirable effects?</td>
<td>Favors intervention</td>
</tr>
<tr>
<td>Values</td>
<td>Does the target population feel the desirable effects are large relative to the undesirable effects?</td>
<td>Probably yes</td>
</tr>
<tr>
<td></td>
<td>Is there important variability in how patients value the outcomes?</td>
<td>Probably not important uncertainty or variability</td>
</tr>
<tr>
<td>Acceptability</td>
<td>Is the intervention acceptable to key stakeholders?</td>
<td>Yes</td>
</tr>
<tr>
<td>Resource Use</td>
<td>Is the intervention a reasonable and efficient allocation of resources?</td>
<td>Yes</td>
</tr>
<tr>
<td>Equity</td>
<td>What would be the impact of the intervention on health equity?</td>
<td>Probably increased</td>
</tr>
<tr>
<td>Feasibility</td>
<td>Is the intervention feasible to implement?</td>
<td>Yes</td>
</tr>
</tbody>
</table>
### EtR Framework

**Summary: Work Group Interpretations**

<table>
<thead>
<tr>
<th>Balance of consequences</th>
<th>Undesirable consequences clearly outweigh desirable consequences in most settings</th>
<th>Undesirable consequences probably outweigh desirable consequences in most settings</th>
<th>The balance between desirable and undesirable consequences is closely balanced or uncertain</th>
<th>Desirable consequences probably outweigh undesirable consequences in most settings</th>
<th>Desirable consequences clearly outweigh undesirable consequences in most settings</th>
<th>There is insufficient evidence to determine the balance of consequences</th>
</tr>
</thead>
</table>

- Undesirable consequences clearly outweigh desirable consequences in most settings
- Undesirable consequences probably outweigh desirable consequences in most settings
- The balance between desirable and undesirable consequences is closely balanced or uncertain
- Desirable consequences probably outweigh undesirable consequences in most settings
- Desirable consequences clearly outweigh undesirable consequences in most settings
- There is insufficient evidence to determine the balance of consequences
**EtR Framework**  
**Summary: Work Group Interpretations**

<table>
<thead>
<tr>
<th>Type of recommendation</th>
<th>We do not recommend the intervention</th>
<th>We recommend the intervention for individuals based on shared clinical decision-making</th>
<th>We recommend the intervention</th>
</tr>
</thead>
</table>
Considerations for Use
Clinical Guidance

▪ **Use in IC adults**
  – RZV may be used irrespective of prior receipt of varicella vaccine or zoster vaccine live

▪ **Dosing schedule**
  – First dose at Month 0 followed by a second dose 2 to 6 months later
  – For individuals who are or will be immunodeficient or immunosuppressed and who would benefit from a shorter vaccination schedule: First dose at Month 0 followed by a second dose 1 to 2 months later
Clinical Guidance, cont.

- **Coadministration with other vaccines**
  - CDC’s general best practice guidelines for immunization advise that recombinant and adjuvanted vaccines, such as RZV, can be administered concomitantly, at different anatomic sites, with other adult vaccines

- **Counseling for reactogenicity**
  - Providers should counsel patients about expected systemic and local reactogenicity before vaccination
Clinical Guidance, cont.

- **Timing of vaccination**
  - If appropriate, vaccinate prior to immunosuppression
  - Otherwise, if possible, consider timing zoster vaccination when immune response is likely to be most robust
  - RZV may be administered while patients are taking antivirals
  - Don’t want to miss the opportunity to vaccinate
Special Populations

- **Persons with a history of herpes zoster**
  - Should receive RZV
  - If experiencing an acute episode, delay vaccination until symptoms abate

- **Pregnancy**
  - Currently no ACIP recommendation for RZV use in pregnancy
  - Consider delaying RZV until after pregnancy
  - Do not recommend pregnancy testing prior to vaccination
Breastfeeding

- CDC’s general best practices for immunization advise that inactivated, recombinant, subunit, polysaccharide, and conjugate vaccines, as well as toxoids, pose no risk for mothers who are breastfeeding or for their infants.
- Therefore, clinicians may consider vaccination without regard to breastfeeding status if otherwise indicated.
Persons with no documented history of varicella or varicella vaccination

- Laboratory testing
  - Commercial IgG ELISAs can be used to assess varicella-zoster virus (VZV) seroconversion after wild type infection; however, sensitivity and specificity can vary
  - No commercially available assays are sensitive and specific enough to reliably detect vaccine seroconversion

- RZV is not indicated for prevention of primary varicella infection, and varicella vaccine is contraindicated for many IC patients
  - Persons born in the U.S. prior to 1980 are considered immune to varicella; however, this criterion does not apply to IC persons
  - Persons born in the U.S. after 1980 and IC persons: Refer to ACIP varicella vaccine recommendations

- Safety data regarding use of RZV in VZV naïve persons is limited
Policy Options and Discussion
Proposed Draft Recommendation

Two doses of recombinant zoster vaccine are recommended for adults aged ≥19 years who are or will be immunodeficient or immunosuppressed due to disease or therapy for the prevention of herpes zoster and its complications.
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The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.
Backup Slides


