Preliminary Evidence to Recommendations Framework Regarding Use of Recombinant Zoster Vaccine in Immunocompromised Adults and Next Steps

ACIP Meeting

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Policy Question

- **Should adults ≥19 years of age 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 conditions, and taking immunosuppressive medications/therapies

Evidence to Recommendations (EtR) Framework: PICO Question

Population	Immunocompromised (IC) adults ≥19 years of age
Intervention	Recombinant zoster vaccine (RZV), 2 doses at least 4 weeks apart
Comparison	No vaccine
Critical Outcomes	• Prevent Herpes Zoster (HZ) • Serious Adverse Events (SAEs)
Important Outcomes	• Prevent Postherpetic Neuralgia (PHN) • Prevent HZ-Related Hospitalization • Immune-Mediated Disease (IMD) • Graft versus Host Disease (HSCT) • Graft Rejection (SOT) • Reactogenicity (Grade 3)

EtR Framework

EtR Domain	Question
Public Health Problem	Is the problem of public health importance?
Benefits and Harms	How substantial are the desirable anticipated effects?
	How substantial are the undesirable anticipated effects?
	Do the desirable effects outweigh the undesirable effects?
Values	Does the target population feel the desirable effects are large relative to the undesirable effects?
	Is there important variability in how patients value the outcomes?
Acceptability	Is the intervention acceptable to key stakeholders?
Feasibility	Is the intervention feasible to implement?
Resource Use	Is the intervention a reasonable and efficient allocation of resources?
Equity	What would be the impact of the intervention on health equity?

EtR Domain: Public Health Problem

Public Health Problem

Is herpes zoster in immunocompromised adults of public health importance?

- Are the consequences of HZ in IC adults serious?
- Are a large number of IC adults affected by HZ?
- Are there IC populations disproportionately affected by HZ?

○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know

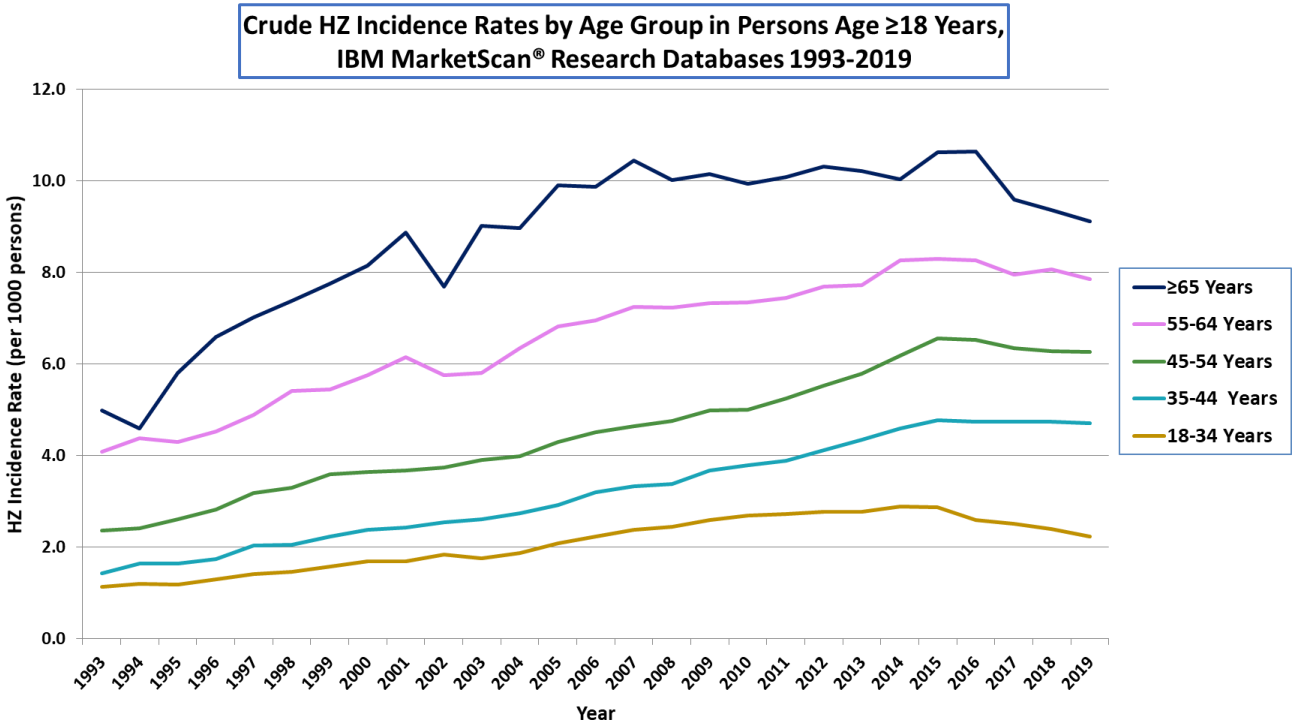
How many IC persons in the United States?*

- **~7 million IC adults[1]**
- **~3 million among:**
  - Hematopoietic stem cell transplant recipients[2]
  - Patients with hematologic malignancies[3]
  - Renal or other solid organ transplant recipients[4]
  - Patients with solid tumor malignancies[3,5]
  - People living with HIV[6]
- **~22 million with autoimmune and/or inflammatory (AI) conditions[7]**
  - >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)

*References on slide 79

HZ Incidence Common in Adults and Increases with Age

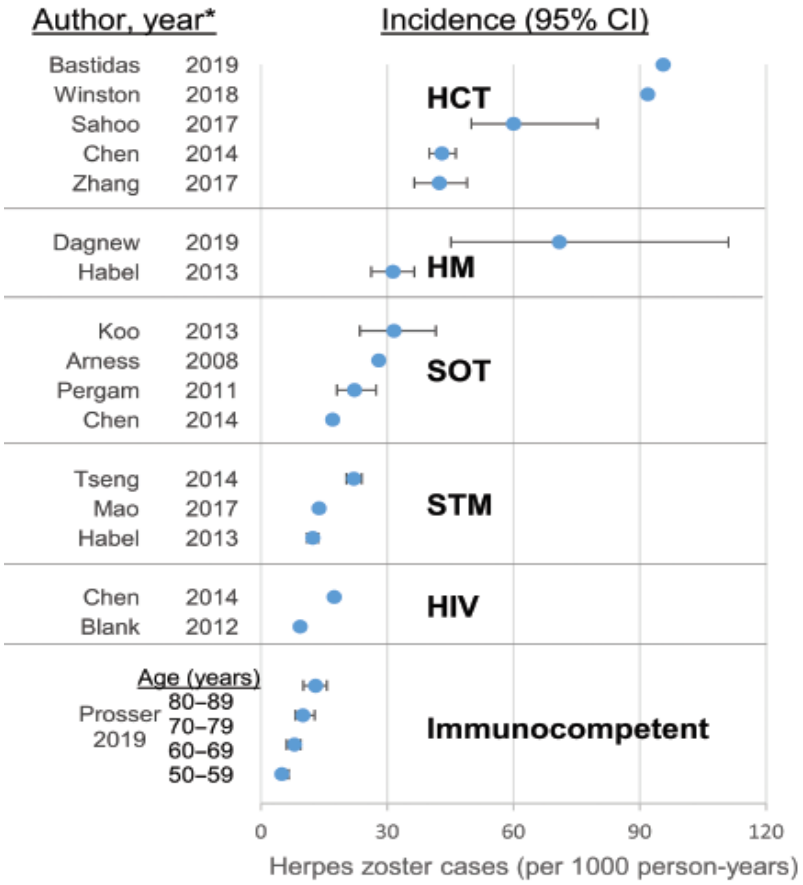
~1 million HZ cases per year in U.S. during pre- HZ vaccine era[1]



1. **Harpaz et al.** Prevention of Herpes Zoster, *MMWR*, June 6, 2008, Vol 57, #5
2. **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**



McKay et al. Herpes zoster risk in immunocompromised adults in the United States: A systematic review. CID 2020;71(7):e125–34.

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)**
  - **~6–10%** vs ~4% overall in administrative claims databases[1]
  - Between **6% and 45%** across IC conditions and studies[2]
- **Disseminated HZ**
  - **~3%**[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]

[1]**Chen et al.** Incidence of herpes zoster in patients with altered immune function. Infection 2014; 42(2): 325–34; [2]**McKay et al.** Herpes zoster risk in immunocompromised adults in the United States: A systematic review. CID 2020;71(7):e125–34; [3]**Rommelaere et al.** Disseminated varicella zoster virus infection in adult renal transplant recipients: Outcome and risk factors. Transplantation Proceedings. 2012; 44(9): 2814-2817; [4]**Kirnap et al.** Prevalence and outcome of herpes zoster infection in renal transplant recipients. Exp Clin Transplant. 2015; Apr;13 Suppl 1:280-3; [5]**Winston et al**. Inactivated varicella zoster vaccine in autologous haemopoietic stem-cell transplant recipients: an international, multicentre, randomised, doubleblind, placebo-controlled trial. Lancet (London, England) 2018; 391(10135): 2116–27; [6]**Izurieta et al.** Effectiveness and duration of protection provided by the live-attenuated herpes zoster vaccine in the Medicare population ages 65 years and older. CID 2017;64(6):785–93.

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]

Age and sex-standardized HZ incidence rates, among adults ≥20 years with selected autoimmune diseases

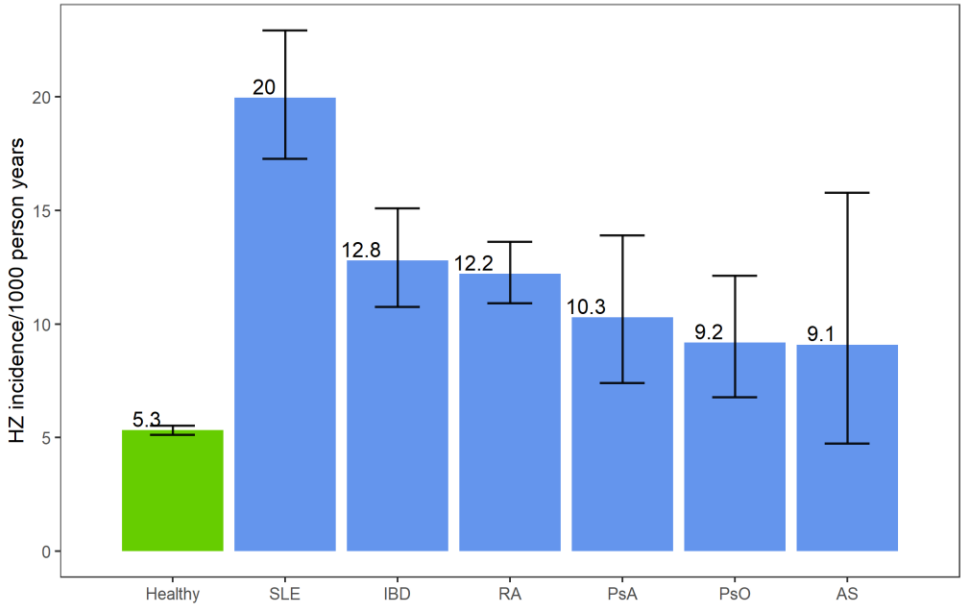


Figure adapted from Yun et al. Bars show the IRs of HZ with 95% confidence intervals. Cohorts of healthy adults without autoimmune diseases or diabetic conditions and adult patients with diabetes were used as controls. SLE=systemic lupus erythematosus; IBD=inflammatory bowel disease; RA=rheumatoid arthritis;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

[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

Group 6 Examples: SLE, IBD, and RA

- **Disease burden**
  - HZ risk ~2 to 4-fold higher
  - Age-specific incidence rates among 21–50-year-olds comparable or substantially higher than corresponding rates in healthy adults >60 years
- **Impact of immunosuppressive treatments**
  - Standard of care for patients to be on ≥1 IC drugs
  - Not possible to define high risk subgroups based on anticipated drugs
    - Disease modifying antirheumatic drugs, or DMARDs (e.g., methotrexate)
    - Glucocorticoids
    - Biologics (e.g., Janus Kinase inhibitors)

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 combination
- Important to consider broad recommendations and provider guidance for IC populations

Public Health Problem:

Work Group Interpretation

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

Benefits and Harms

How substantial are the desirable anticipated effects?

- How substantial is the anticipated effect for each main outcome for which there is a desirable effect?

○ Minimal ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know

Benefits and Harms

How substantial are the undesirable anticipated effects?

- How substantial is the anticipated effect for each main outcome for which there is an undesirable effect?

○ Minimal ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know

Benefits and Harms

Do the desirable effects outweigh the undesirable effects?

- What is the balance between the desirable effects relative to the undesirable effects?

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

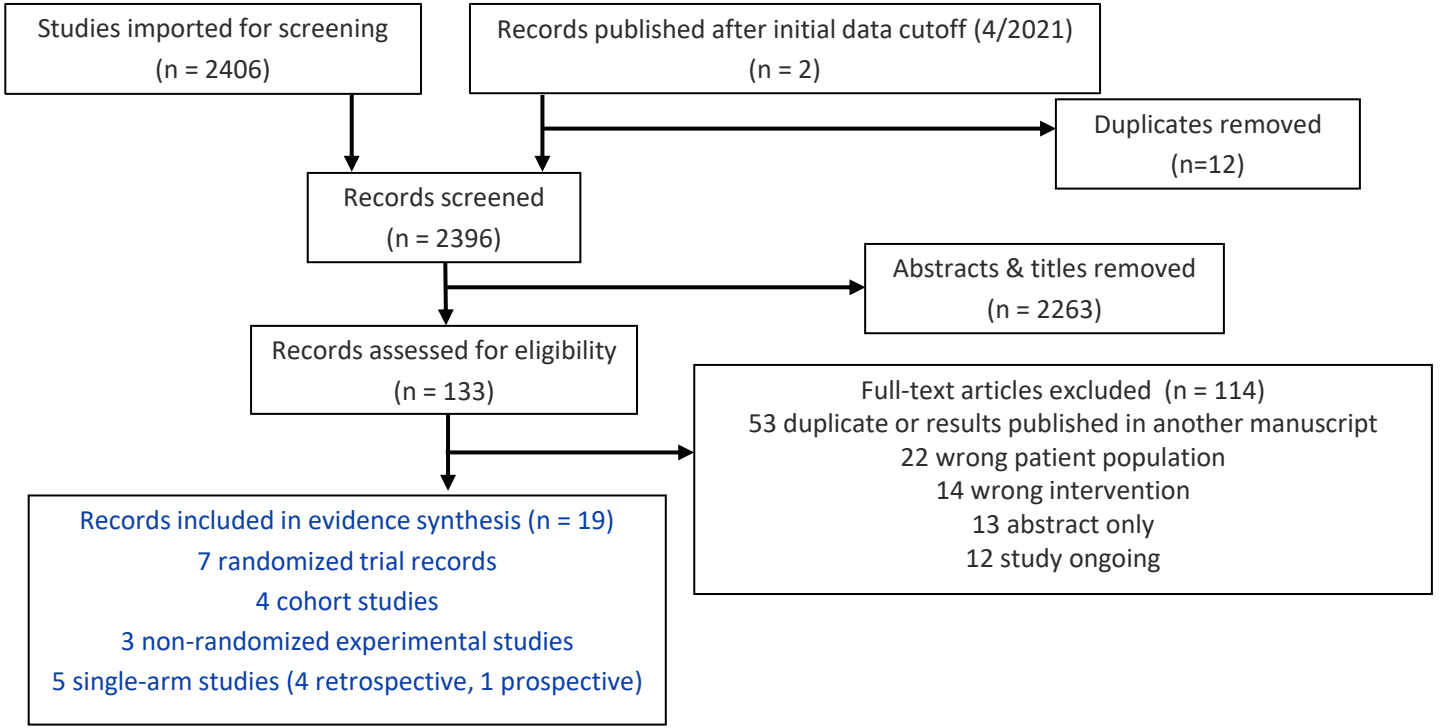
Systematic Review

Information Sources	Inclusion and Exclusion Criteria
• 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 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

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



Appendix 1. Studies Included in the Review of Evidence

Study	Design	Study Population	N Intervention	N Comparison	Outcomes	Funding
Dagnew, 2019	RCT	Patients with hematological malignancy ≥18	283	279	• Immunogenicity • Reactogenicity (including Grade 3) • SAEs and general AEs; potential immune-mediated diseases (pIMDs) • Time to occurrence of confirmed HZ cases	GSK
Vink, 2020	RCT	Renal transplant (RT) patients ≥18	132	132	• Immunogenicity • Reactogenicity (Grade 3) • Number of SAEs; pIMDs • Renal allograft rejection	GSK
Vink, 2019	RCT	Solid Tumor Patients ≥18	102	107	• Immunogenicity • Reactogenicity (Grade 3) • Number of SAEs; pIMDs	GSK
Bastidas, 2019	RCT	Autologous HSCT patients ≥18	922	924	• Number of subjects with HZ & PHN/HZ-associated complications • Immunogenicity • Reactogenicity (Grade 3) • Number of SAEs	GSK
Dagnew, 2021	RCT	Participants pIMDs from ZOE-50/70 not on immunosuppression	983	960	• Efficacy of RZV in preventing HZ (post-hoc) • Occurrence of SAEs; new onset/exacerbations of pIMDs	GSK
Stadtmauer, 2014	RCT	Autologous HCT recipients ≥18	62	30	• Reactogenicity (Grade 3) • Occurrence SAEs; number of subjects with new-onset IMDs • Immunogenicity • Number of confirmed HZ cases	GSK
Berkowitz, 2015	RCT	Patients with HIV ≥18	74	49	• Number of Subjects with SAEs • Reactogenicity (Grade 3) • Immunogenicity • Number of HZ cases and complications	GSK
Khan, 2021	Cohort	Patients with IBD ≥50	4,875	26,549	• Efficacy of RZV in preventing HZ • Efficacy by steroid use	Pfizer
Izurieta, 2021	Cohort	Medicare Beneficiaries aged ≥65 with IC/AI Conditions	AI: 61,999 IC: 40,442	IC: 746,654 AI: 886,123	• Vaccine efficacy of RZV in preventing HZ	FDA, CMS

Outcomes for GRADE

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

Evidence type: 1=high; 2=moderate; 3=low; 4=very low; ND, no data

Outcome 1: Prevent Herpes Zoster (HZ)
Randomized Studies with Unvaccinated Comparator (n=5)

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

* 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 was calculated using Wald Confidence Intervals in Epitools in R and in SAS.

Outcome 1: Prevent HZ
Observational Studies with Unvaccinated Comparator (n=2)

Study	Design	Population	n/N (Vaccinated)	n/n (Unvaccinated)	VE (%) (95% CI)	Study Limitations
Izurieta, 2021	Prospective cohort	Medicare patients ≥65				Serious*
		• Autoimmune condition	167/61,999 (0.27%)	20,640/886,123 (2.33%)	68.0% (62.3 - 72.8)	
		• Immuno-compromised	143/40,442 (0.35%)	18,504/746,654 (2.48%)	64.1% (57.2 - 69.8)	
Khan, 2021	Retrospective cohort	VAHS patients with IBD ≥50	8/4,875 (0.16%)	337/26,549 (1.27%)	Hazard Ratios reported below**	Serious ***
		• 50-60 subset	• 0/655 (0.0%)	• 69/5,995 (1.15%)	• No steroid use: NE • Steroid use: NE	
		• >60 subset	• 8/4,220 (0.19%)	• 268/20,554 (1.30%)	• No steroid use: 0.41 (0.19-0.87) • Steroid use: 0.34 (0.05-2.44)	

* 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 did not report VE, but rather 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;P¼.01) 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: Prevent HZ – Immunogenicity as Surrogate Randomized Studies with Unvaccinated Comparator (n=6)

			Humoral Immunity		Cell-mediated Immunity		
Study	Population	Timing after last dose	% Response Rate RZV (95% CI)	% Response Rate Placebo (95% CI)	% Response Rate RZV (95% CI)	% Response Rate Placebo (95% CI)	Adjusted Humoral GMR (95% CI)
Bastidas, 2019	Autologous HSCT patients ≥18	1 Month	67%	0%	93%	0%	-
		12 Months	-	-	-	-	
Berkowitz, 2015	Patients with HIV ≥18*	1 Month	96.2% (87-99.5%)	2.8% (0.1-14.5%)	90% (68.3-98.8%)	16.7% (3.6-41.4%)	-
		12 Months	91.7% (80-97.7%)	0% (0-9.5%)	64.5% (45.4-80.8%)	0% (0-13.2%)	-
Dagnew, 2019	Patients with hematological malignancy ≥18	1 Month	65.4% (58.7-71.7%)	0.5% (0.0-2.8%)	83.7% (69.3-93.2%)	6.8% (1.4-18.7%)	29.75 (21.09–41.96)
		12 Months	52.1% (44.2-59.9%)	3.6% (1.2-8.1%)	66.7% (48.2-82.0%)	6.5% (0.8-21.4%)	-
Stadtmauer, 2014	Autologous HCT recipients ≥18	1 Month	-	-	-	-	42.20 (16.07-110.82)
		12 Months	-	-	-	-	8.81 (3.41-22.80)
Vink, 2019	Solid Tumor Patients ≥18	1 Month	86.2%	0.0%	50.0%	0.0%	14.4 (10.7-19.5)**
		12 Months	51.5%	0.0%	17.6%	0.0%	-
Vink, 2020	Renal transplant patients ≥18	1 Month	80.2%	4.2%	71.4%	0.0%	14.00 (10.90–17.99)***
		12 Months	66.7%	6.4%	56.7%	0.0%	-

*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: Prevent HZ

Certainty Assessment							Number of Patients (%)		Effect		
#	Study Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other	RZV 2 doses	No vaccine	Relative (95%)	Certainty	Importance
Prevent Herpes Zoster (HZ)											
5	RCT	not serious	not serious	Serious**	not serious	none	• ≥18 years: 0% to 5.6% of participants experienced HZ. • ≥50 years: 0.43% to 6.1% of participants experienced HZ.	• ≥18 years, 0% to 15.9% of participants experienced HZ. • ≥50 years, 4.12% to 16.6% of participants experienced HZ.	• ≥18 years, **VE ranged from 68.2% (95% CI: 55.6-77.5%) to 87.2% (44.3-98.6%)**, Stadtmauer reported an RR of 0. • ≥50 years, **VE ranged from 67% (53-78%) to 90.5% (73.5-97.5%).**	Type 2 Moderate	CRITICAL
6	RCT* – Immuno-genicity	not serious	not serious	very serious***	not serious	none	• Humoral VRR ranged from 65.4% to 96.2% • Cell-mediated VRR ranged from 50% to 93%.	• Humoral VRR ranged from 0% to 4.2% and cell-mediated VRR ranged from 0% to 16.7%	• Humoral adjusted GMR ranged from **14.00 (95% CI: 10.90-17.99) to 42.20 (16.07-110.82)** • Cell-mediated adjusted GMR ranged from **9.94 (3.63-27.19) to 17.26 (5.92-50.36).**	Type 3 Low	
2	Cohort	not serious	not serious	serious****	not serious	Strong assoc.	• ≥65 years, AI condition: 167/61,999 (0.27%) experienced HZ • ≥65 years, IC condition: 143/40442 (0.35%) experienced HZ. • 50-60 years: 0/655 (0.0%) experienced HZ • >60 years: 8/4220 (0.19%) experienced HZ	• ≥65 years, AI condition: 20,640/ 886,123 (2.33%) experienced HZ • ≥65 years, IC condition: 18,504/746,654 (2.48%) experienced HZ. • 50-60 years: 69/5,995 (1.15%) experienced HZ • >60 years: 268/20,554 (1.30%) experienced HZ	• ≥65 years, AI condition: **VE was 68.0% (62.3 - 72.8%)** • ≥65 years, IC condition**: VE was 64.1% (57.2 - 69.8%)** • **50-60 years, HR was 0, >60 years, HR was 0.39 (0.19-0.80)**	Type 3 Low	

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

**The RCTs cover a wide range of populations that cover some, but not all of 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)

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

*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

Certainty assessment							№ of patients (%)		Effect	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	RZV	Comparison	Relative (95% CI)		
Serious adverse events											
7	RCT	not serious	not serious	serious*	not serious	none	SAEs ranged from **8.1% to 39.3**%	SAEs ranged from **4.1% to 39.1%**	• RR ranged from **0.79 to 1.99** • 3 studies reported RR < 1 • 1 study reported RR = 1 • 3 studies reported RR >1	Type 2 Moderate	CRITICAL

*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).

Outcome 7: Graft Rejection
Randomized Studies with Unvaccinated Comparator (n=1)

Study	Population	Events/ Vaccine (n/N) (%)	Events/ Placebo (n/N) (%)	RR (95% CI)*	Study Limitations
Vink, 2020	Patients with renal transplant ≥18 receiving daily immunosuppressive therapy	4/132 (3.0%)**	7/132 (5.3%)**	0.57 (0.17, 1.91)	Not serious

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

**Graft rejection events were reported from 30 days after last vaccination through the study end in the table above, with 0/132 events reported in both the vaccine and placebo group for the time period from the first vaccination through 30 days after the last vaccination.

Outcome 7: Graft Rejection
Studies with No Comparator (n=3)

- **Barghash, 2020** (Retrospective chart review, heart transplant patients)
  - 0/65 (0%) & 0/46 (0%) of patients experienced rejection after 1st & 2nd dose, respectively
- **L'Huillier, 2021** (non-randomized experimental study, solid organ transplant patients)
  - No rejection occurred in the 3 months following vaccination, however, most patients were several years posttransplant, when the risk of rejection is lower.
- **Hirzel, 2021** (non-randomized experimental study, lung transplant recipients)
  - 3 participants (3/49, 6.1%) experienced 4 rejection episodes (4/49, 8.2%). All within the first year post-transplant. One lung transplant recipient had 2 episodes of clinically suspected rejection 89 and 130 days after the first vaccination (both episodes before the second vaccine dose). Due to the long interval between suspected rejection and RZV immunization, these rejection episodes were classified as unrelated to vaccination.

Outcome 7 Evidence Table: Graft Rejection

Certainty assessment							№ of patients		Effect		
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RZV	Comparison	Relative (95% CI)	Certainty	Importance
Graft Rejection											
1	RCT	not serious	not serious	serious*	serious**	none	4/132 (3.0%)	7/132 (5.3%)	0.57 (0.17, 1.91) **	Type 3 Low	IMPORTANT

*This study only provides data regarding renal transplant patients, which does not cover the entire patient population for which graft rejection is a potential harm (i.e., other solid organ transplants). Thus, this study is downgraded (-1) for indirectness.
**These results were downgraded for imprecision due to the not meeting the optimal information size with only 11 total events occurring, and wide confidence intervals crossing the harm/benefit threshold.

Summary of GRADE

Outcome	Importance	Design (# of studies)	Findings	Evidence Type
Benefits				
Prevent Herpes Zoster (HZ)	Critical	RCT(5) OBS(2)	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.	Type 2
Prevent Postherpetic Neuralgia (PHN)	Important	RCT(1)	VE of 89% (12%-100%)	Type 3
Prevent HZ-Related Hospitalization	Important	RCT(1)	VE of 85% (32%-97%)	Type 3
Harms				
Serious adverse events (SAE)	Critical	RCT(7)	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.	Type 2
- Immune-Mediated Disease	Important	RCT(5)	Not increased in RZV group: RRs ranged from 0.68 to 2.0 but confidence intervals included null effect.	Type 3
- Graft vs. Host Disease (HCT)	Important	RCT(1)	Not increased in RZV group: RR of 0.83 (0.21, 3.24)	Type 3
- Graft Rejection (SOT)	Important	RCT(1)	Not increased in RZV group: RR of 0.57 (0.17, 1.91)	Type 3
Reactogenicity (Grade 3)	Important	RCT(6)	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.	Type 2

Evidence type: 1=high; 2=moderate; 3=low; 4=very low; ND, no data

Benefits and Harms:

Work Group Interpretation

How substantial are the desirable anticipated effects?

○ Minimal ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know

Benefits and Harms:

Work Group Interpretation

How substantial are the undesirable anticipated effects?

○ 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

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

-How does the target population view the balance of desirable versus undesirable effects?

-Would patients feel that the benefits outweigh the harms and burden?

-Does the population appreciate and value RZV?

○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know

Values

Is there important uncertainty about, or variability in, how much people value the main outcomes?

-How much do individuals value each outcome in relation to the other outcomes?
-Is there evidence to support those value judgments?
-Is there evidence that the variability is large enough to lead to different decisions?

- ○ Important uncertainty or variability
- ○ Probably important uncertainty or variability
- ○ Probably not important uncertainty or variability
- ○ No important uncertainty or variability
- ○ No known undesirable outcomes

Values

Available evidence and work group discussions

- Limited published data
- In general
  - Zoster vaccination is increasing[1,2]
  - Series completion rates are high[3,4]
- Although there is no recommendation, IC patients recognize the increased risk of HZ and many have already received RZV[3]

[1]**Terlizzi EP and Black LI**. Shingles Vaccination Among Adults Aged 60 and Over: United States, 2018. NCHS Data Brief, No. 370, July 2020; [2]**Kawai K and Kawai AT**. Racial/Ethnic and Socioeconomic Disparities in Adult Vaccination Coverage. Am. J. Prev. Med. 2021;000(000):1–9; [3]**Izurieta et al.** Recombinant Zoster Vaccine (Shingrix): Real-World Effectiveness in the First 2 Years Post-Licensure. Clin. Infect. Dis. 2021 Sep 15;73(6):941-948; [4]**Patterson et al**. Early examination of real-world uptake and second-dose completion of recombinant zoster vaccine in the United States from October 2017 to September 2019. Hum. Vaccin. Immunother. 2021 Aug 3;17(8):2482-2487.

Summary

- IC patients desire the ability to receive RZV to prevent HZ and its complications
- Many IC patients already pursuing vaccination with RZV
- Anticipate more IC patients would pursue vaccination for HZ if recommended by ACIP and their provider

Values:

Work Group Interpretation

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

○ No	○ Probably no	○ Probably yes	○ Yes	○ Varies	○ Don't know

Values:

Work Group Interpretation

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

Acceptability

Is recombinant zoster vaccine acceptable to key stakeholders?

- Are there key stakeholders that would not accept the distribution of benefits and harms?

- Are there key stakeholders that would not accept the undesirable effects in the short term for the desirable effects (benefits) in the future?

○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know

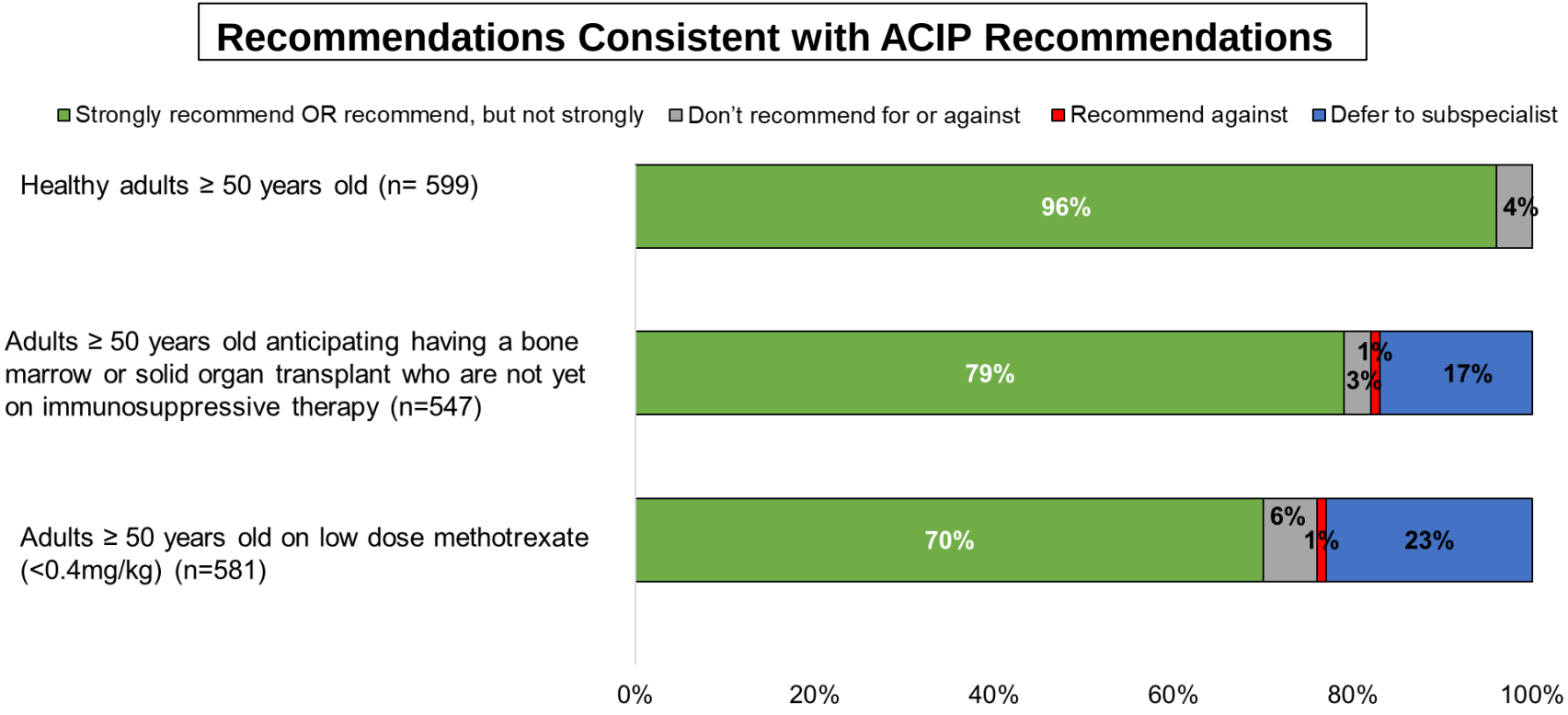
Is the Intervention Acceptable to Key Stakeholders?

- **Available evidence**
  - Limited published data
  - Primary care physicians' perspective captured in 2020 University of Colorado Denver knowledge, attitudes, and practices survey
- **Work Group discussions**
  - IC populations are very heterogeneous, both across and within groups and among individuals over time
  - It is not feasible to define every possible IC condition and therapy combination, thus it is important to consider broad recommendations and provider guidance for IC groups
  - An age-based recommendation is preferred since this will provide the most actionable guidance to clinicians and patients

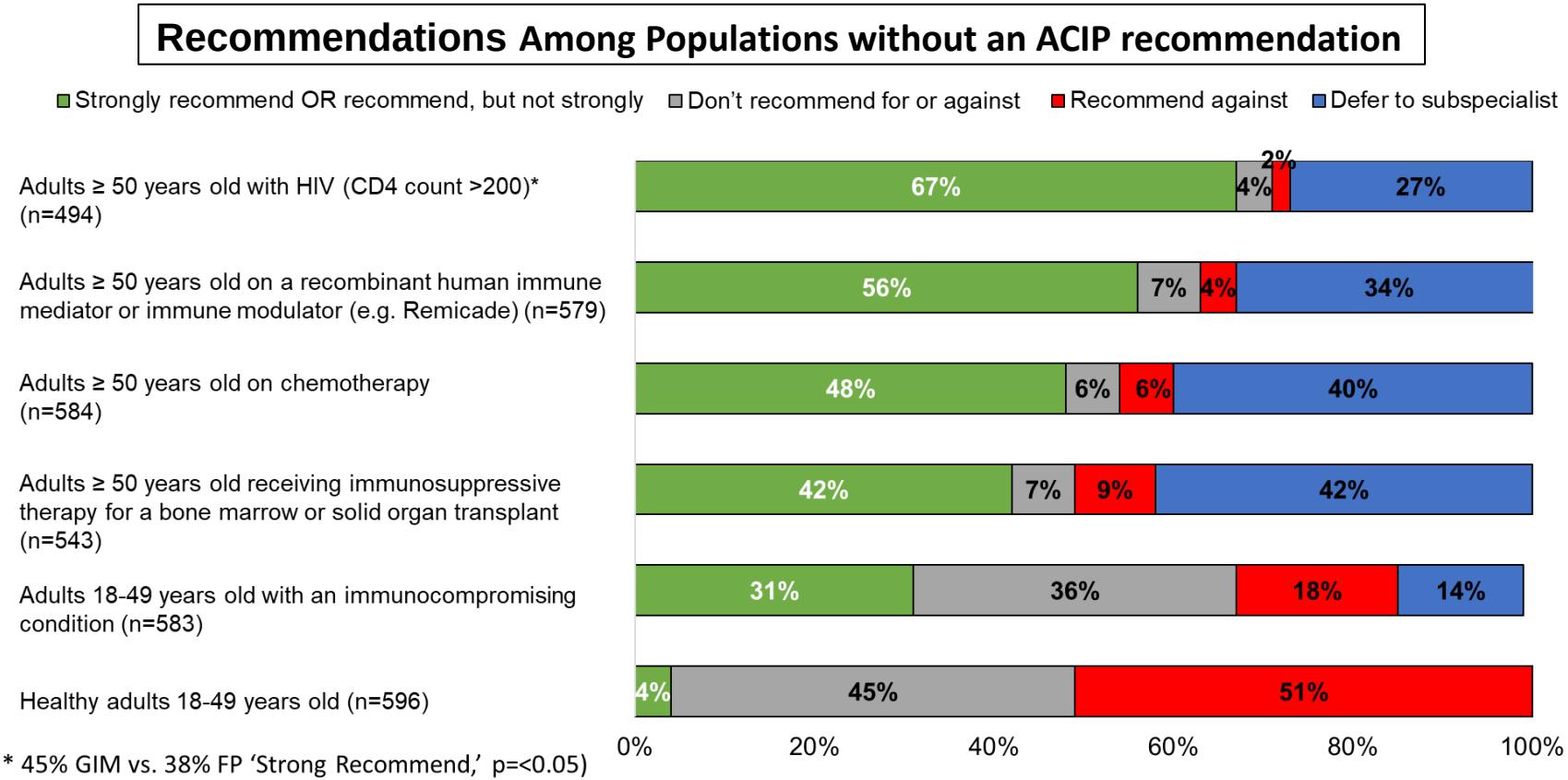
Primary Care Physicians' Perspective Related to Recombinant Zoster Vaccine, 2020

- **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

Physician Strength of Recommendation for RZV in Different Types of Patients, United States, 2020

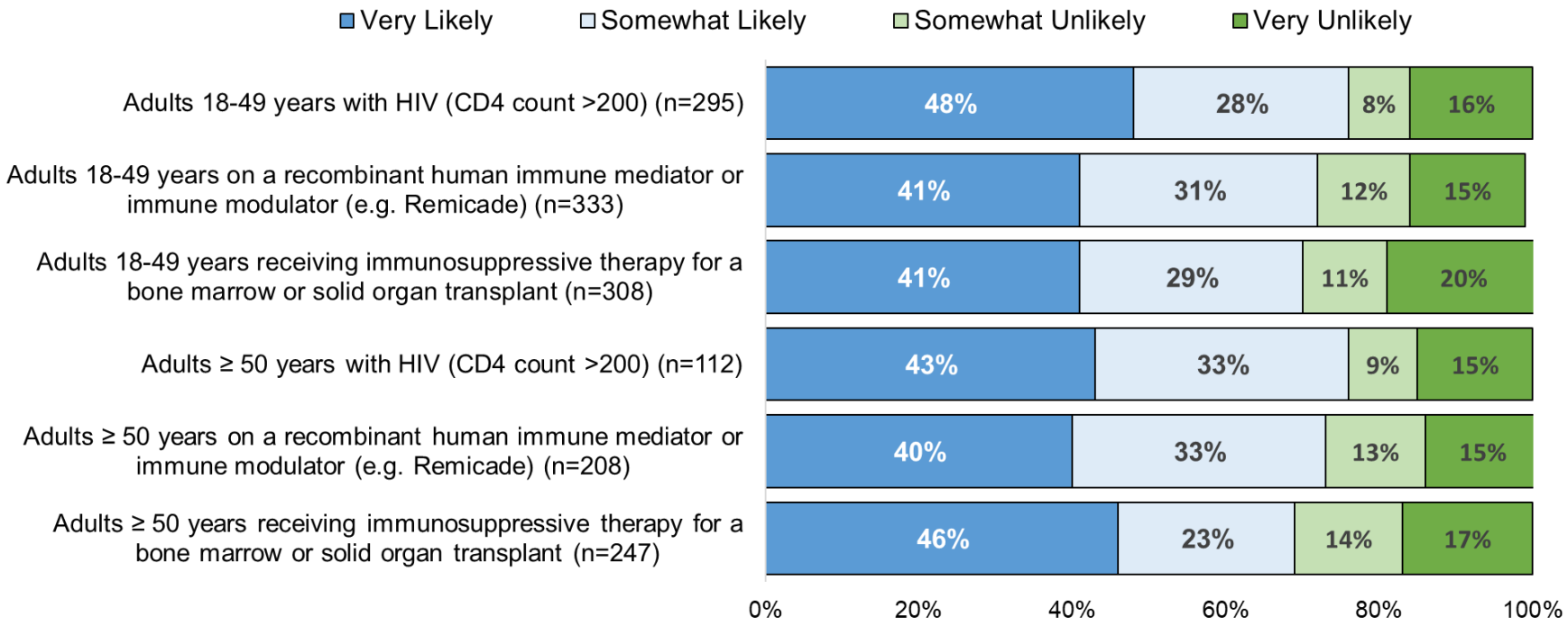


Physician Strength of Recommendation for RZV in Different Types of Patients, United States, 2020 (n=632)



* 45% GIM vs. 38% FP 'Strong Recommend,' p=<0.05)

Likelihood of Recommending RZV to Different Types of IC Patients Among Physicians Who Had Not Recommended RZV to IC Patients*



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

Summary

- **Given highly specialized care and increased HZ risk among IC populations, work group noted that vaccination is favored if there are no safety concerns**
  - As previously noted, 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)
- **Anticipate would increase with FDA approval and ACIP recommendation**

Acceptability:

Work Group Interpretation

Is recombinant zoster vaccine acceptable to key stakeholders?

○ No	○ Probably no	○ Probably yes	○ Yes	○ Varies	○ Don't know

EtR Domain: Feasibility

Feasibility

Is RZV in immunocompromised adults feasible to implement?

- Is the RZV vaccination program sustainable?
- Are there barriers that are likely to limit the feasibility of implementing RZV vaccination or require consideration when implementing it?
- Is access to RZV an important concern?

○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know

Is the Intervention Feasible to Implement?

- **Available evidence**
  - Limited published data
  - Primary care physicians' perspective captured in 2020 University of Colorado Denver Knowledge, Attitudes, and Practices Survey
- **Work Group discussions**
  - IC populations are very heterogeneous, both across and within groups and among individuals over time
  - It is not feasible to define every possible IC condition and therapy combination, thus it is important to consider broad recommendations and provider guidance for IC groups.
  - An age-based recommendation is preferred since this will provide the most actionable guidance to clinicians and patients

Summary

- **Delivery of RZV is complicated by delivery at different locations**
  - As previously noted, physicians need more direction on which of their patients are eligible for RZV
  - Anticipate identification of IC patients (e.g., based on immunosuppressive medications) and standing orders will be concerns in the pharmacy setting

- **Although implementation is addressed at the Jurisdiction and Provider levels, decision support guidance (e.g., for EHRs, immunization registries, etc.) would be helpful**

Feasibility:

Work Group Interpretation

Is RZV in immunocompromised adults feasible to implement?

○ No	○ Probably no	○ Probably yes	○ Yes	○ Varies	○ Don't know

EtR Domain: Resource Use

Resource Use

Is RZV a reasonable and efficient allocation of resources?

- What is the cost-effectiveness of RZV in IC adults?

- How does the cost-effectiveness of RZV change in response to changes in context, assumptions, etc.?

○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know

Cost-Effectiveness Assessments

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

*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.

Summary

- **Base-case: HSCT patients**
  - Economic value of RZV appears to be *favorable* (i.e., cost-saving)
  - High(er) 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 is 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
- **Given highly specialized care and resources invested for base-case and other IC populations, work group did not consider cost-effectiveness assessments to be a main driver for decision-making**

Resource Use:

Work Group Interpretation

Is RZV a reasonable and efficient allocation of resources?

○ No	○ Probably no	○ Probably yes	○ Yes	○ Varies	○ Don't know

EtR Domain: Equity

Equity

What would be the impact of RZV on health equity?

- Are there groups or settings that might be disadvantaged in relation to herpes zoster burden or receipt of RZV?

- Are there considerations that should be made when implementing the RZV vaccination program to ensure that inequities are reduced whenever possible, and that they are not increased?

○ Reduced ○ Probably reduced ○ Probably no impact
○ Probably increased ○ Increased ○ Varies ○ Don't know

What Would be the Impact of the Intervention on Health Equity?

- **2018 NHIS data[1]**
  - 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[2]**
  - In general, race/ethnicity, household income, education level, and health insurance type significantly associated with receipt of zoster vaccinations among adults aged ≥65 years

[1]**Lu P, Hung M, Srivastav A, et al**. Surveillance of Vaccination Coverage Among Adult Populations — United States, 2018. MMWR Surveill Summ 2021;70(No. SS-3):1–26; [2]**Kawai K and Kawai AT**. Racial/Ethnic and Socioeconomic Disparities in Adult Vaccination Coverage. Am. J. Prev. Med. 2021;000(000):1–9.

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
  - potential out of pocket costs

Equity:

Work Group Interpretation

What would be the impact of RZV on health equity?

○ Reduced ○ Probably reduced ○ Probably no impact
○ Probably increased ○ Increased ○ Varies ○ Don't know

Overall EtR Summary

EtR Framework

EtR Domain	Question	Work Group Judgments
Public Health Problem	Is the problem of public health importance?	**Yes**
Benefits and Harms	How substantial are the desirable anticipated effects?	**Large**
	How substantial are the undesirable anticipated effects?	**Small**
	Do the desirable effects outweigh the undesirable effects?	**Favors intervention**
Values	Does the target population feel the desirable effects are large relative to the undesirable effects?	**Probably yes**
	Is there important variability in how patients value the outcomes?	**Probably not important uncertainty or variability**
Acceptability	Is the intervention acceptable to key stakeholders?	**Yes**
Feasibility	Is the intervention feasible to implement?	**Yes**
Resource Use	Is the intervention a reasonable and efficient allocation of resources?	**Yes**
Equity	What would be the impact of the intervention on health equity?	**Probably increased**

EtR Framework
Summary: Work Group Interpretations

Balance of consequences	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

Type of recommendation	We do not recommend the intervention	We recommend the intervention for individuals based on shared clinical decision-making	We recommend the intervention

Special Considerations and Next Steps

RZV Package Insert Contraindications, Warnings and Precautions

- **Contraindications:** History of severe allergic reaction to any component of the vaccine or after a previous dose of Shingrix
- **Warnings and Precautions**
  - In a postmarketing observational study, an increased risk of Guillain-Barré syndrome (GBS) was observed during the 42 days following vaccination with SHINGRIX.
  - Syncope (fainting) can be associated with the administration of injectable vaccines, including SHINGRIX.

Special Considerations

- **Pregnancy**
  - **Package insert:** The data are insufficient to establish if there is vaccine-associated risk with SHINGRIX in pregnant women.
  - **Work group discussion:** Do not recommend pregnancy testing prior to vaccination; if known pregnancy, delay vaccination (given lack of data)
- **Breastfeeding**
  - **Package insert:** Data are not available to assess the effects of SHINGRIX on the breastfed infant or on milk production/excretion; The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for SHINGRIX and any potential adverse effects on the breastfed child from SHINGRIX or from the underlying maternal condition.
  - **Work group discussion:** Similar to most other vaccine recommendations, do not recommend delaying vaccination

Special Considerations, cont.

- **Individuals with a history of GBS**
  - Update VIS “Risks of a vaccine reaction” section per FDA package insert warning
  - Providers and patients should discuss potential risk
- **Individuals who have received the varicella vaccine series**
  - Laboratory testing not recommended to confirm vaccine-induced immunity
- **Individuals with no history of varicella or varicella vaccine**
  - RZV not indicated for prevention of primary varicella infection
  - Laboratory testing not recommended to confirm naïve
  - Limited safety data

Next Steps

- Today's discussion focused on the preliminary EtR and special considerations
- HZWG to discuss ACIP feedback and finalize the EtR
- Final EtR and vote anticipated at future ACIP meeting

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Thank You

For more information, contact CDC
1-800-CDC-INFO (232-4636)
TTY: 1-888-232-6348 www.cdc.gov

Backup Slides

Slide 7 References

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