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

ACIP Meeting

October 20, 2021

LCDR Tara Anderson, DVM, MPH, PhD
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

Population	Immunocompromised (IC) adults aged ≥19 years
Intervention	Recombinant zoster vaccine (RZV), 2 doses at least 4 weeks apart*
Comparison	No vaccine
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.

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?
Resource Use	Is the intervention a reasonable and efficient allocation of resources?
Equity	What would be the impact of the intervention on health equity?
Feasibility	Is the intervention feasible to implement?

EtR Domain: Public Health Problem

How many IC persons in the United States?

- **~7 million adults with self-reported immunosuppressed status**

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

Harpaz R, Dahl RM, Dooling KL. Prevalence of Immunosuppression Among US Adults, 2013, JAMA, 2016, 316(23):2547-8.
Excerpt of Table. Self-reported Immunosuppressed Status.

How many IC persons in the United States?*

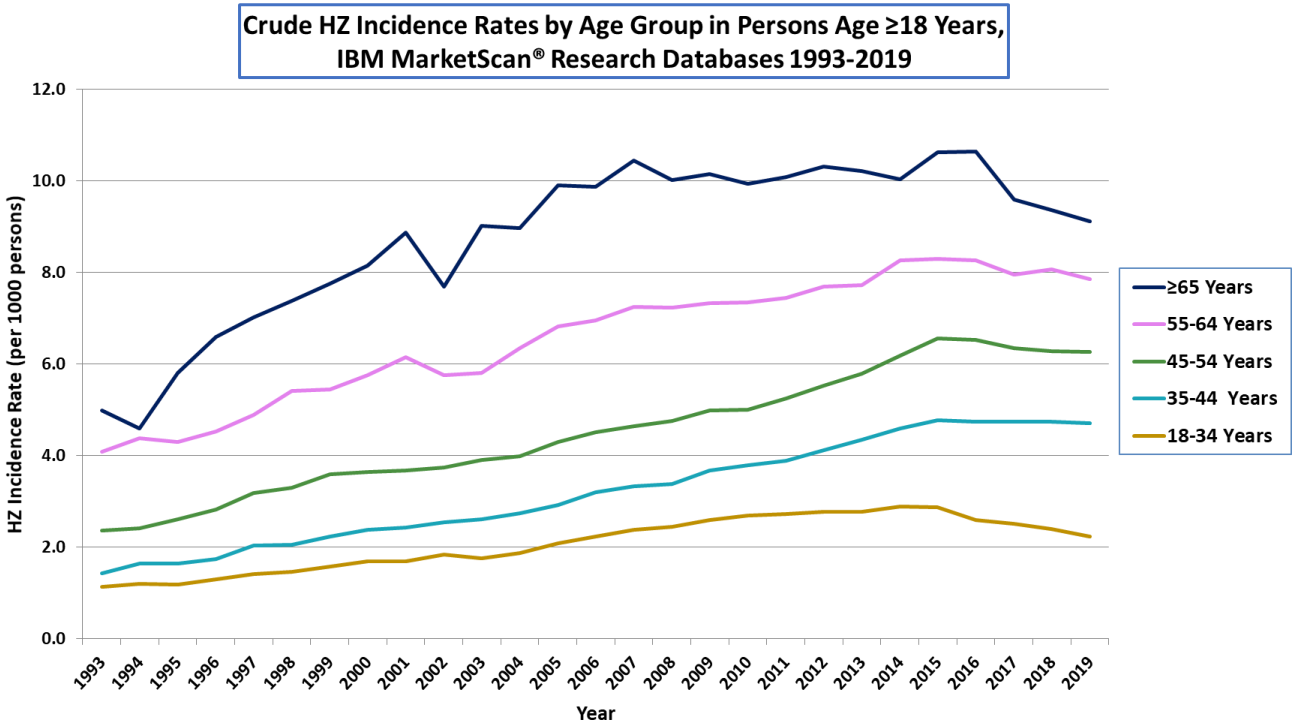
- **~3 million among:**
  - Hematopoietic stem cell transplant recipients[1]
  - Patients with hematologic malignancies[2]
  - Renal or other solid organ transplant recipients[3]
  - Patients with solid tumor malignancies[2,4]
  - People living with HIV[5]
- **~22 million with autoimmune and/or inflammatory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



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

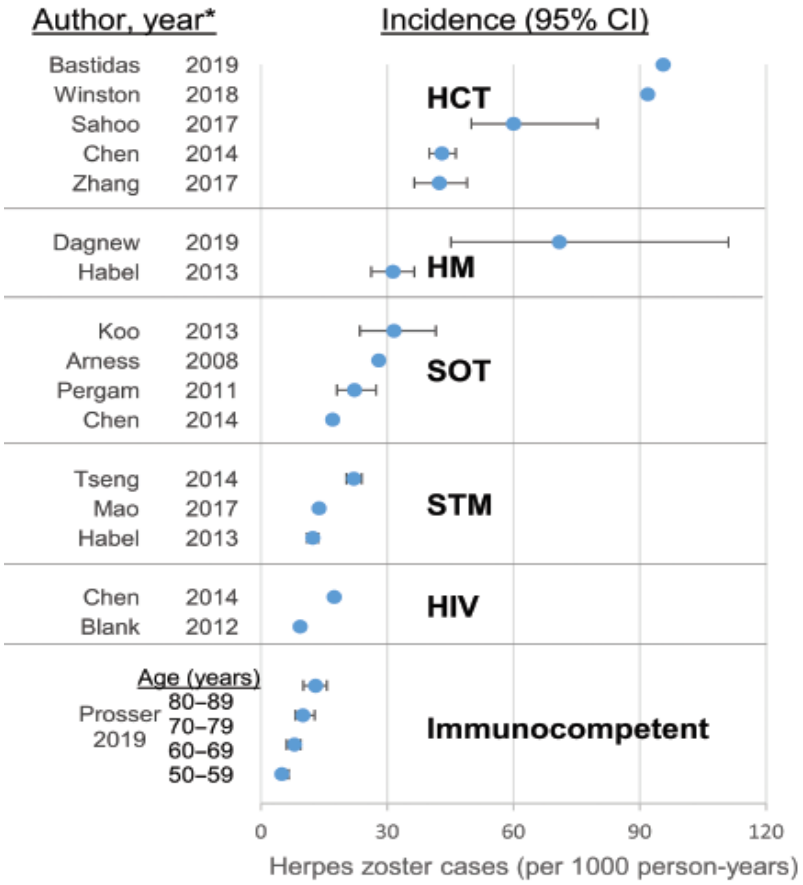


Figure 3. Herpes zoster incidence rates among patients with selected immunocompromising conditions. *Studies with low or medium risk of bias.

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

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

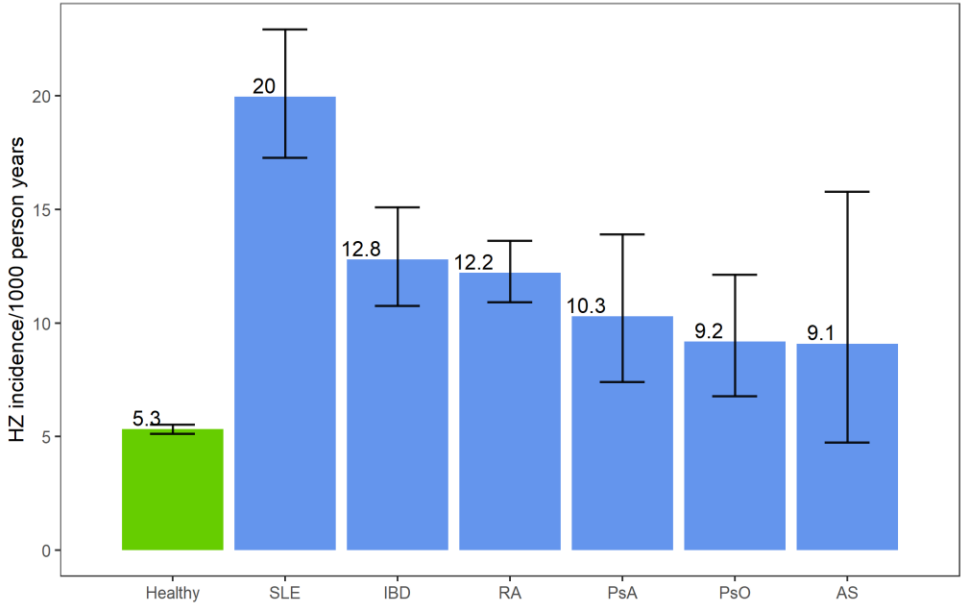


Figure adapted from Yun et al. Bars show the IRs of HZ with 95% confidence intervals. Cohorts of healthy adults without autoimmune diseases or diabetic conditions and adult patients with diabetes were used as controls. SLE=systemic lupus erythematosus; IBD=inflammatory bowel disease; RA=rheumatoid arthritis;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

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 antirheumatic drugs, or DMARDs (e.g., methotrexate)
    - Glucocorticoids
    - Biologics (e.g., Janus Kinase inhibitors)

Incidence Rate (per 1000 person years) of HZ reported in different disease cohorts[8]

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

Healthy = individuals without AI/IC conditions or diabetes; SLE = systemic lupus erythematosus; IBD = inflammatory bowel disease; RA = Rheumatoid arthritis; PsO = Psoriasis; PsA = Psoriatic Arthritis

Reference
Higher Risk
Comparable Risk

* **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

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

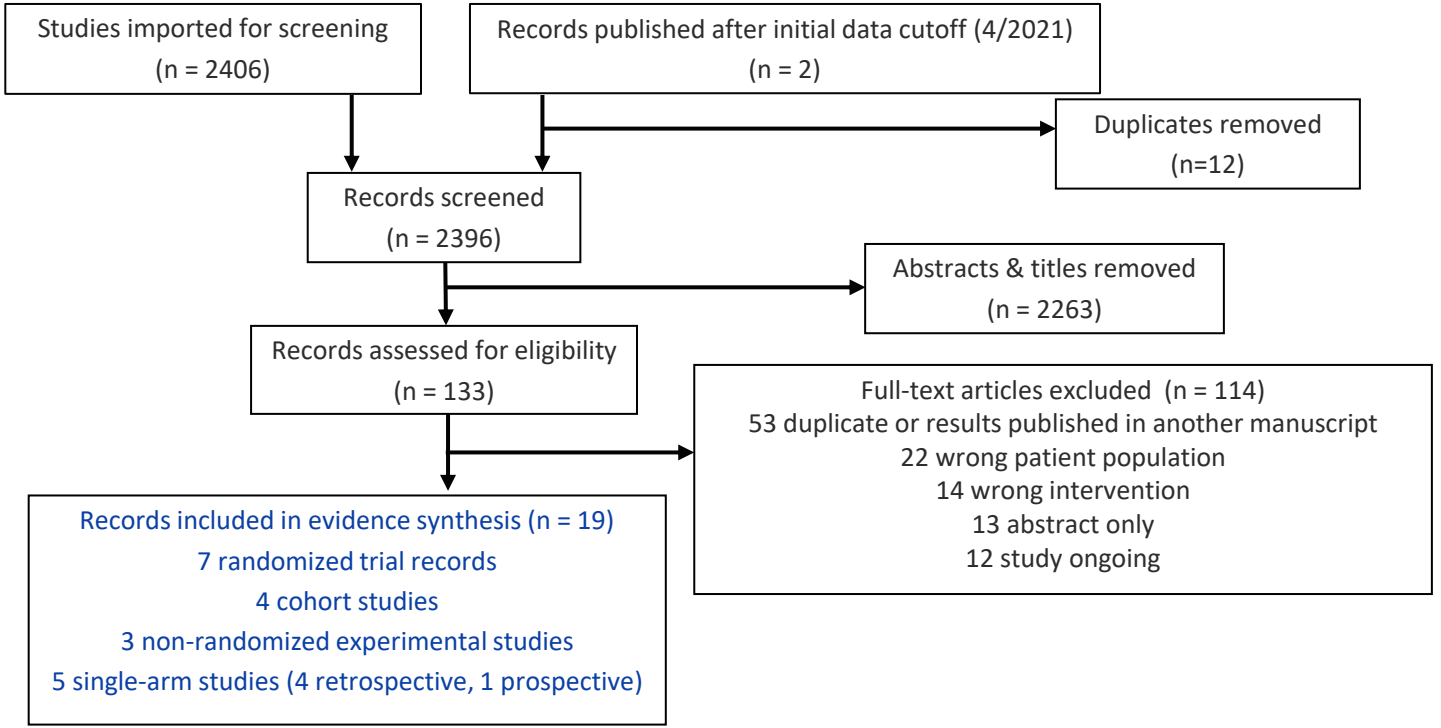
Systematic Review

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	Study design	Country	Study Population, Age	N Intervention	N comparison	Outcomes	Funding
Bastidas, 2019	Phase III RCT	Multiple countries, including US	Autologous HSCT recipients ≥18 years	• 1 dose: 922 • 2 doses: 870	• 1 dose: 924 • 2 doses: 851	• 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 • 2 doses: 72 • 3 doses: 71	• 1 dose: 49 • 2 doses: 47 • 3 doses: 47	• Confirmed HZ • Immunogenicity • Reactogenicity • SAEs	GSK
Dagnew, 2019	Phase III RCT	Multiple countries, including US	Patients with hematological malignancy ≥18 years	• 1 dose: 283 • 2 doses: 259	• 1 dose: 279 • 2 doses: 257	• Confirmed HZ • Immunogenicity • Reactogenicity • SAEs (including Graft vs. Host Disease, pIMDs)	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 2 doses: 936	• 1 dose: 960 • 2 doses: 923	• 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 2 doses: 31	• 3 doses: 30	• Confirmed HZ • Immunogenicity • Reactogenicity • SAEs, pIMDs	GSK
Vink, 2019	Phase II/III RCT	Canada, Czech Republic, France, Korea, Spain, United Kingdom	Solid tumor patients ≥18 years	• 1 dose: 117 • 2 doses: 102	• 1 dose: 115 • 2 doses: 107	• Immunogenicity • Reactogenicity • SAE, pIMDs	GSK
Vink, 2020	Phase III RCT	Belgium, Canada, Finland, Taiwan, Spain, Panama, Korea, Italy	Renal transplant patients ≥18 years receiving daily immunosuppressive therapy	• 1 dose: 132 • 2 doses: 131	• 1 dose: 132 • 2 doses: 132	• Immunogenicity • Reactogenicity • SAEs (including graft rejection, pIMDs)	GSK
Izurieta, 2021	Cohort Study	United States	Medicare beneficiaries ≥65 years with IC or AI conditions	• AI 1 dose: 92,069 • IC 1 dose: 60,600 • AI 2 doses: 61,999 • IC 2 doses: 40,442	• AI: 886,123 • IC: 746,654	• 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 • ≥60: 4,220	• 50–60: 5,995 • ≥60: 20,554	• 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

Outcome	Importance	Design (# of studies)	Findings	Evidence Type
Benefits				
Herpes Zoster (HZ)	Critical	RCT(5) OBS(2)		
Postherpetic Neuralgia (PHN)	Important	RCT(1)		
HZ-Related Hospitalization	Important	RCT(1)		
Harms				
Serious adverse events (SAE)	Critical	RCT(7)		
- Immune-Mediated Disease	Important	RCT(6)		
- 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: 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%)	NE	NE	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 and Wald confidence intervals calculated in R and in SAS.

Outcome 1: Herpes Zoster (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 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: 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: Herpes Zoster

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 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 HSCT 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 (0.60, 1.05) to 1.99 (0.42, 9.44),** with 3 studies reporting RR <1, 3 studies reporting RR>1, and one reporting 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).

Summary of GRADE

Outcome	Importance	Design (# of studies)	Findings	Evidence Type
Benefits				
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
Postherpetic Neuralgia (PHN)	Important	RCT(1)	VE of 89% (12%-100%)	Type 3
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(6)	Not increased in RZV group: RRs ranged from 0.68 to 2.0 but confidence intervals included null effect.	Type 4
- Graft vs. Host Disease (HSCT)	Important	RCT(1)	Not increased in RZV group: RR of 0.83 (0.21, 3.24)	Type 4
- 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 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]

[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.

Values, cont.

- **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**

* 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

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

Values:

Work Group Interpretation

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

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

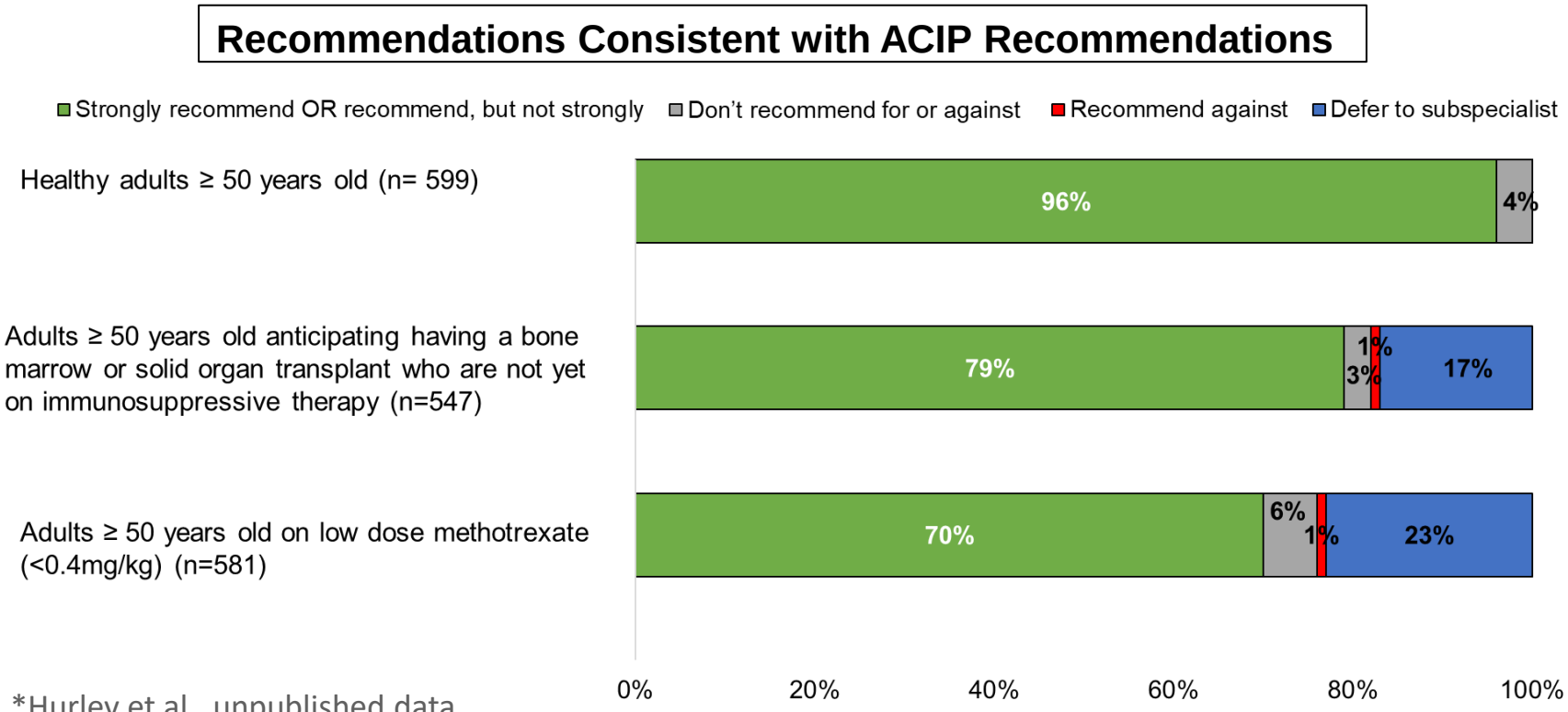
EtR Domain: Acceptability

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

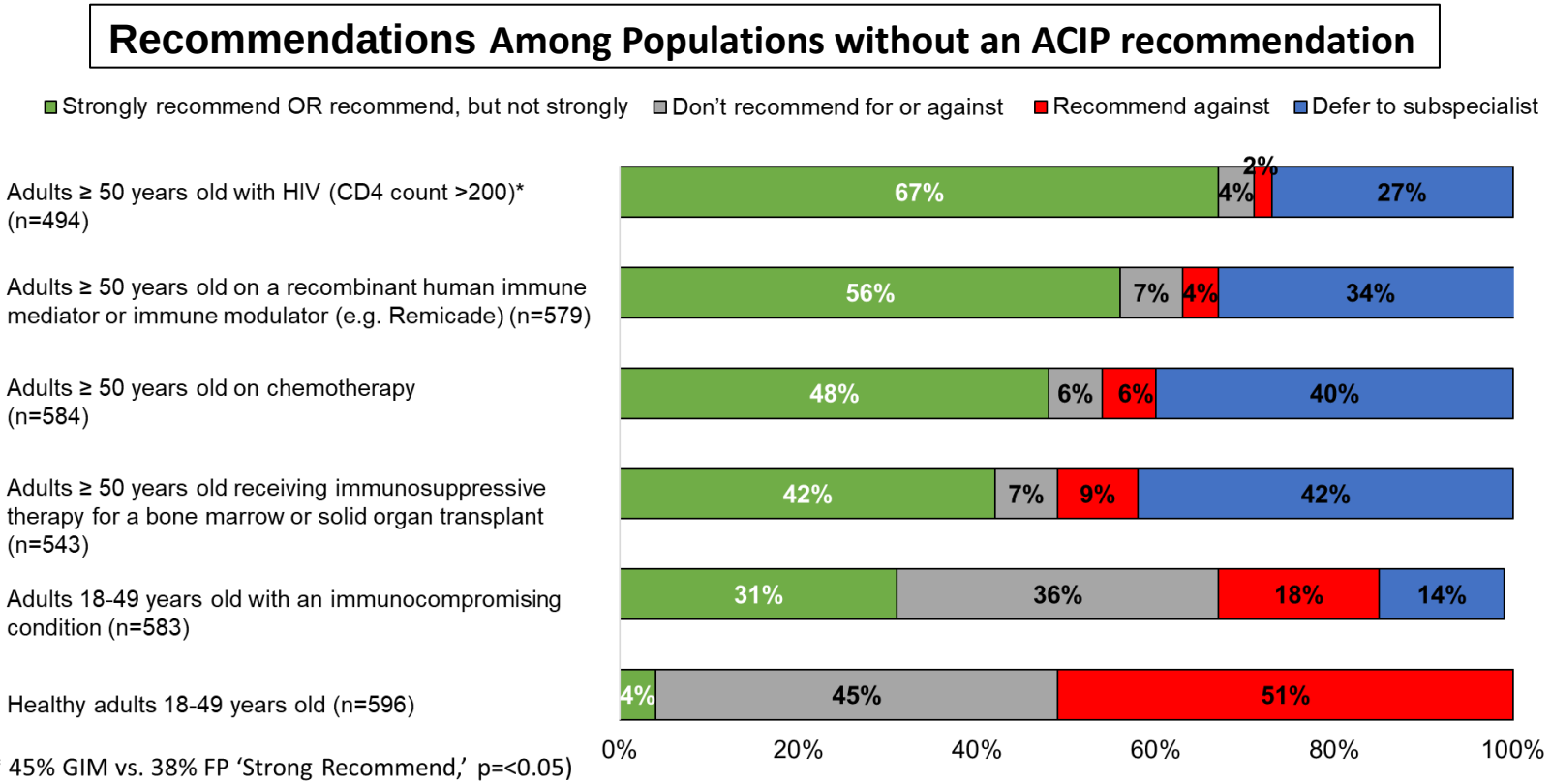
*Hurley et al., unpublished data

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



*Hurley et al., unpublished data

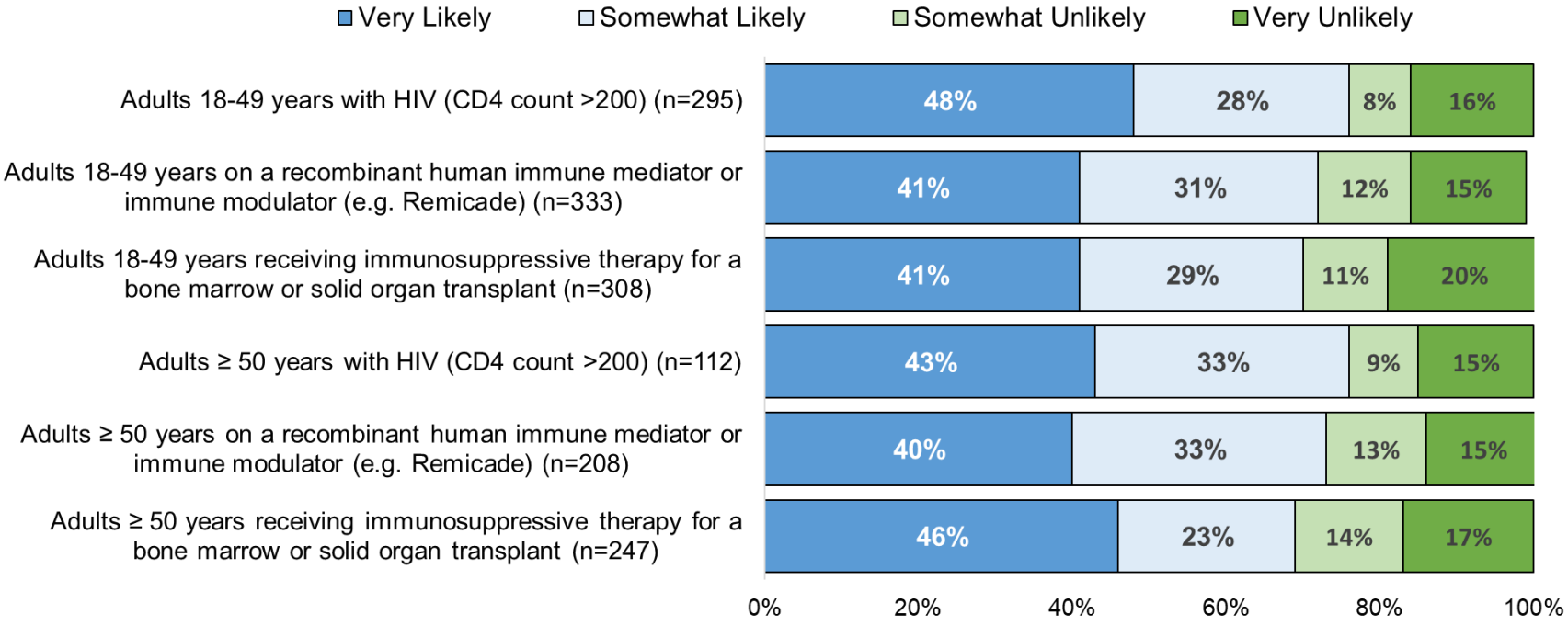
Physician Strength of Recommendation for RZV in Different Types of Patients, United States, 2020 (n=632)



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

*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*



*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

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.

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[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
  - 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?

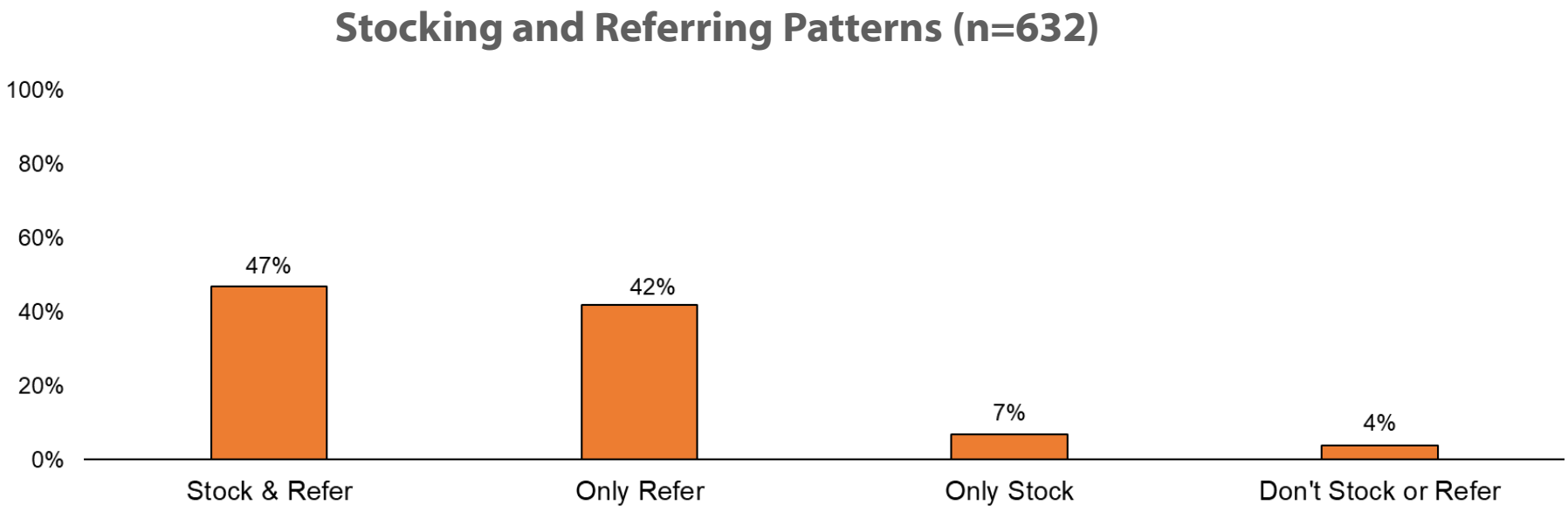
○ Reduced ○ Probably reduced ○ Probably no impact
○ Probably increased ○ Increased ○ Varies ○ Don't know

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.

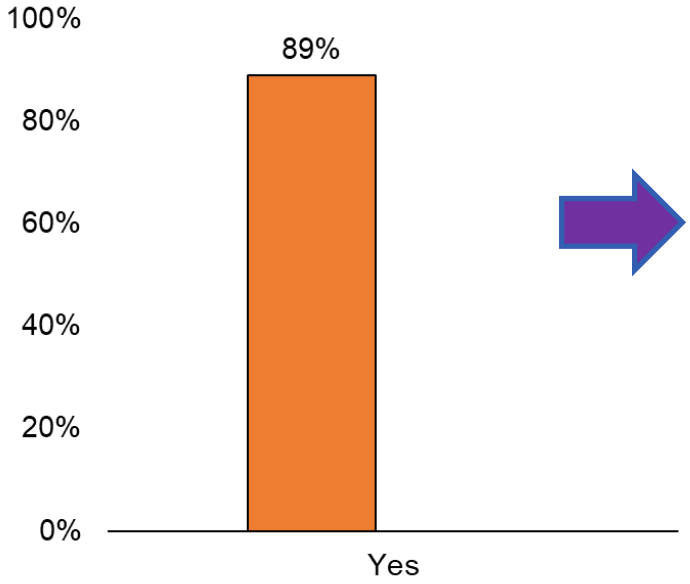
Primary Care Physicians' Perspective Related to Recombinant Zoster Vaccine, 2020



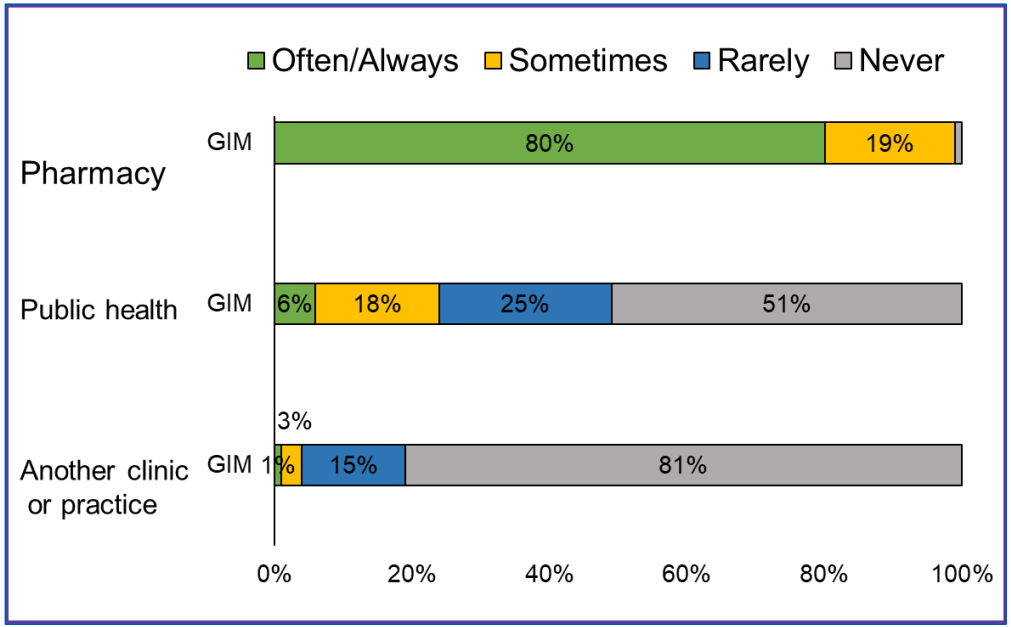
Physicians from smaller (median: 5 providers) and private practices were less likely to stock RZV than larger practices or HMO or hospital-based clinics (p=<0.001).

*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

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**
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**
Feasibility	Is the intervention feasible to implement?	**Yes**

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

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

Special Populations, cont.

- **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

Special Populations, cont.

- **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.

Acknowledgments

- **CDC**
  - Kathleen Dooling
  - Angela Guo
  - Kai Hong
  - Andrew Leidner
  - Jessica Leung
  - Megan Lindley
  - Jessica MacNeil
  - Nina Masters
  - Ismael Ortega-Sanchez
  - Jamison Pike
  - Leah Shepersky
  - Joanna Taliano
- **Herpes Zoster Work Group**
- **GRADE Consultants**
  - Doug Campos-Outcalt
  - Rebecca Morgan
- **University of Colorado Denver, Vaccine Policy Collaborative Initiative**
  - Allison Kempe
  - Laura P. Hurley
  - Lori A. Crane
  - Sean T. O'Leary
  - Michaela Brtnikova
  - Jessica Cataldi
  - Brenda L. Beaty
  - Carol Gorman

Thank You

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

Backup Slides

Slide 8 References

1. D'Souza A, Fretham C. Current Uses and Outcomes of Hematopoietic Cell Transplantation (HCT): CIBMTR Summary Slides, 2018. Available at https://www.cibmtr.org.
2. American Cancer Society, https://cancerstatisticscenter.cancer.org; 2019 incidence estimates.
3. United Network for Organ Sharing, https://unos.org/data/transplant-trends/#transplants_by_organ_type+year; 2018, Renal= Kidney + Kidney/Pancreas, Solid organ = all listed.
4. Halpern MT, Yabroff KR, Cancer Invest, 2008, 26(6):647-51; Derived from Halpern and Yabroff 2000-2004 data on chemo/radiotherapy among all patients with cancers, adjusted based on proportion of all cancers in 2007 due to solid organ cancers, further adjusted by projections that solid cancers increased by 20% between 2007 and 2018 (data from American Cancer Society website).
5. CDC, https://www.cdc.gov/hiv/statistics/overview/ataglance.html; 2017 incidence, 2016 prevalence of diagnosed HIV infections.
6. Derived from Hayter SM. Autoimmun Rev. 2012 Aug;11(10):754-65 (prevalence 4.5% for all conditions excluding psoriasis) and Rachakonda TD. J Am Acad Dermatol. 2014 Mar;70(3):512-6 (prevalence of 3.2% for psoriasis alone), applied to projected adult US population in 2020 (US Census: 289.6 million).