Zoster Vaccine Session:
Risk of Guillain-Barré syndrome following herpes zoster

ACIP Meeting

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Guillain-Barré syndrome (GBS)

- **Rare immune-mediated disease of the peripheral nerves**
- **Estimated annual incidence in U.S. across all ages: 1–2/100,000 persons**
- **Risk factors**
  - Increasing age
  - Male gender
  - Immunocompromised status
  - Previous infections
    - Viral infections: CMV, EBV, influenza, hepatitis E, Zika
    - Bacterial infections: *Campylobacter jejuni*, *Mycoplasma pneumoniae*
  - Recent vaccinations (e.g., some influenza and rabies vaccines)

What is the risk of GBS following herpes zoster (HZ)?

- **Possible temporal association between HZ and GBS noted in small number of case reports**
- **One previous epidemiologic study (Kang, Sheu, and Lin, 2010) reported an increased risk of GBS following recent HZ**
  - Population-based cohort study using Taiwan's National Health Insurance Research Database
  - Found 0.03% of patients developed GBS within two months following HZ
  - Adjusted hazard of GBS during follow-up period was 18.37 (95% CI, 10.22–33.01) times greater for patients with HZ than those without HZ
- **No published epidemiologic studies in other settings or using other methods**

Risk of GBS following HZ, United States, 2010–2018

- **Case series study, designed to:**
  - Strengthen epidemiologic understanding of risk of GBS following HZ
  - Help clarify benefits vs. potential risks of vaccination
- **Primary Objective:** Evaluate risk of GBS following HZ using a self-controlled case series analysis of healthcare claims data from two large national data sources
- **Secondary Objective:** Describe characteristics of these GBS cases
  - Demographics
  - Outcome severity (e.g., duration of GBS hospitalization, ICU admission)

Self-Controlled Case Series (SCCS) Methodology

- Developed in 1995 for use in vaccine safety studies; has been broadly applied in epidemiology
- Used to examine the temporal association between a transient exposure (e.g., HZ) and a subsequent event (e.g., GBS); precise timing of the exposure and event is important
- Only individuals with both the exposure and the event of interest are included in the analysis
- Each case serves as their own control; therefore, confounding by time-invariant factors is eliminated
- SCCS method estimates the relative risk of rates in the risk window compared to rates in the control window(s)

Data Sources

IBM MarketScan® Commercial

- Individual-level, de-identified, healthcare claims for persons covered by employer-sponsored insurance
- Convenience sample drawn from IBM Watson Health's clients
- ~30–50 million persons enrolled annually since 2006

CMS Medicare

- Individual-level, de-identified, healthcare claims information for Medicare beneficiaries
- 100% sample of all clinical claims data from Medicare
- ~50–60 million Medicare enrollees annually, among whom 34–37% are enrolled in Medicare A/B/D

Study Populations

MarketScan Commercial

- 2010–2018 MarketScan Commercial Claims and Encounters (CCAE) data
- Persons aged 18–64 years with private health insurance with drug data supplied
- Enrolled in MarketScan 180 days before through 365 days after HZ index date

CMS Medicare

- 2014–2018 CMS Medicare data
- Persons aged ≥65 years with Medicare insurance with Parts A, B, and D
- Enrolled in Medicare 180 days before through 365 days after HZ index date

Study Exposure Definitions: HZ

- **Persons with ICD-9 or ICD-10 outpatient claim with primary or secondary diagnostic code for HZ**
  - Exclude persons in whom first HZ code is a code for post-herpetic neuralgia (PHN); Retain persons with subsequent PHN codes
  - Exclude persons with claim for administration of any zoster vaccine within one day of the HZ claim (HZ diagnostic code likely miscoding error)
  - Exclude persons with HZ claims during the prior 180-day period
  - HZ index date defined as date of first HZ claim during the study period

Study Outcome Definitions: GBS

- **Persons with ICD-9 or ICD-10 inpatient claim for GBS as the principle diagnostic code**
  - Must be accompanied by typical procedural codes (i.e., lumbar puncture, electromyography, or nerve conduction study) for patients with GBS
  - Excluded persons with GBS in 180 days before HZ
  - Excluded persons with select previous infections and Shingrix 42 days prior to GBS
    - Select viral infections: CMV, EBV, influenza, hepatitis E, Zika
    - Select bacterial infections: *Campylobacter jejuni, Mycoplasma pneumoniae*

Study Outcome Definitions: Negative Controls

- **Selected conditions similar to GBS (i.e., acute, frequently result in hospitalization, low rate of reoccurrence) that were not expected to increase after HZ**
  - Appendicitis
  - Nephrolithiasis
  - Cholecystitis
  - Fractures of upper limb
- **Defined based on ICD-9 and ICD-10 codes**
- **Excluded persons with claims for these conditions in 180 days prior to HZ**

Study Design

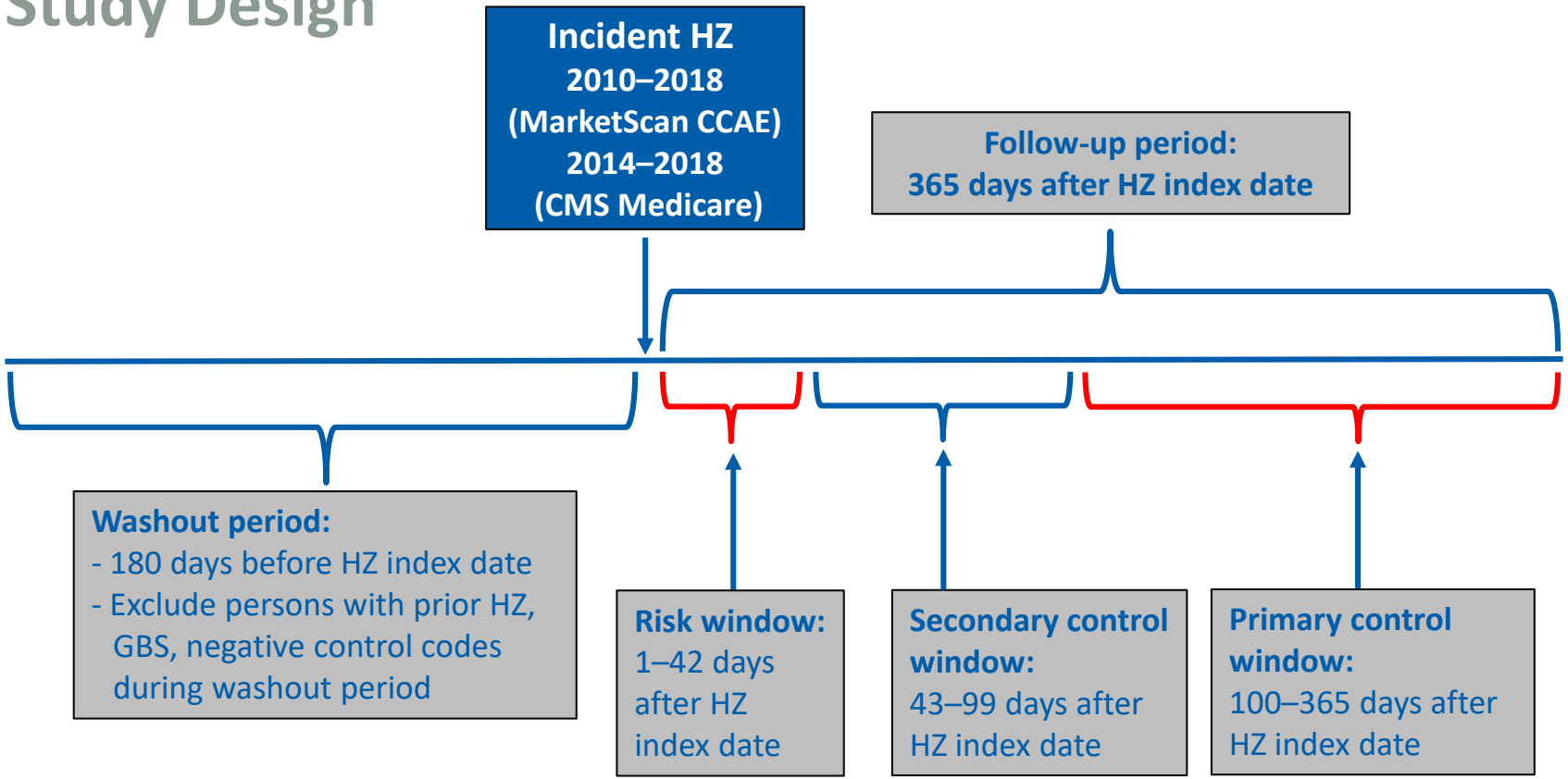

Table 1. Characteristics of persons with HZ and GBS in MarketScan Commercial (CCAE) (2010–18) and CMS Medicare (2014–18) data

	MarketScan CCAE		CMS Medicare	
# GBS Cases	11		41	
Age group (years)				
18–49	5	45%	----	
50–64	6	55%	----	
65–69	----		DS*	----
70–79	----		25	61%
80+	----		DS	----

*DS: Data suppressed (cell size <11 for CMS Medicare data)

Table 1. Characteristics of persons with HZ and GBS in MarketScan Commercial (CCAE) (2010–18) and CMS Medicare (2014–18) data (cont.)

	MarketScan CCAE		CMS Medicare	
# GBS Cases	11		41	
	#	%	#	%
Gender				
Male	2	18%	19	46%
Female	9	82%	22	54%
Interval between HZ and GBS (days after HZ)				
1–42 days	5	45%	11	27%
43–99 days	1	9%	13	32%
100–180 days	0	0%	DS*	----
181–240 days	1	9%	DS	----
241–365 days	4	36%	11	27%

*DS: Data suppressed (cell size <11 for CMS Medicare data)

Table 1. Characteristics of persons with HZ and GBS in MarketScan Commercial (CCAE) (2010–18) and CMS Medicare (2014–18) data (cont.)

	MarketScan CCAE		CMS Medicare	
# GBS Cases	**11**		**41**	
	#	**%**	**#**	**%**
Outcomes				
Duration GBS hospitalization (days) [median (range)]	6 (3–19)		9 (1–27)	
ICU admission	4	36%	21	51%

Table 2. Self-controlled case series analysis results for GBS following HZ using MarketScan Commercial CCAE (2010–18) and CMS Medicare (2014–18) data

	Number of HZ cases	Risk Window	Control Windows			
		Cases 1–42 days after HZ	Primary (Cases 100–365 days after HZ)		Secondary (Cases 43–99 days after HZ)	
Group	**#**	**#**	**#**	**Rate Ratio (95% CI)**	**#**	**Rate Ratio (95% CI)**
MarketScan CCAE (N=489,516 HZ cases)						
GBS	11	5	5	**6.3 (1.8–21.9)**	1	6.8 (0.8–58.1)
CMS Medicare (N= 650,229 HZ Cases)						
GBS	41	11	17	**4.1 (1.9–8.7)**	13	1.1 (0.5–2.6)

Table 2 cont. Self-controlled case series analysis results for negative controls following HZ using MarketScan Commercial CCAE (2010–18) data

	Number of HZ cases	Risk Window	Control Windows			
		Cases 1–42 days after HZ	Primary (Cases 100–365 days after HZ)		Secondary (Cases 43–99 days after HZ)	
Group	#	#	#	Rate Ratio (95% CI)	#	Rate Ratio (95% CI)
MarketScan CCAE (N=489,516 HZ cases)						
Appendicitis	281	38	202	1.2 (0.8–1.7)	41	1.3 (0.8–2.0)
Nephrolithiasis	214	26	159	1.0 (0.7–1.6)	29	1.2 (0.7–2.1)
Cholecystitis	443	49	332	0.9 (0.7–1.3)	62	1.1 (0.7–1.6)
Fractures upper limb	3,994	463	2,898	1.0 (0.9–1.1)	633	1.0 (0.9–1.1)

Table 2 cont. Self-controlled case series analysis results for negative controls following HZ using CMS Medicare (2014–18) data

	Number of HZ cases	Risk Window	Control Windows			
		Cases 1–42 days after HZ	Primary (Cases 100–365 days after HZ)		Secondary (Cases 43–99 days after HZ)	
Group	#	#	#	Rate Ratio (95% CI)	#	Rate Ratio (95% CI)
CMS Medicare (N= 650,229 HZ Cases)						
Appendicitis	316	37	225	1.0 (0.7–1.5)	54	0.9 (0.6–1.4)
Nephrolithiasis	279	44	194	1.4 (1.0–2.0)	41	1.5 (1.0–2.2)
Cholecystitis	1,496	221	1,054	1.3 (1.1–1.5)	221	1.4 (1.1–1.6)
Fractures upper limb	12,375	1,560	8,959	1.1 (1.0–1.2)	1856	1.1 (1.1–1.2)

Strengths and Limitations

- **Strengths**
  - Used large, national datasets that include medical and pharmacy claims
  - SCCS design inherently controls for potential confounders (e.g., gender, underlying medical conditions), and each case serves as their own control
  - Inclusion criteria strengthen HZ and GBS case identification, and exclusion criteria account for potential confounders (e.g., antecedent infections)
- **Limitations**
  - Small numbers of GBS cases
  - MarketScan is a convenience sample, not nationally representative
  - Potential miscoding/misclassification bias in claims data
  - Unable to validate GBS, HZ, or other diagnoses using medical record review

Conclusions

- **Increased risk of GBS 1–42 days following HZ compared to primary control window**
  - Across adult age groups
  - In two different administrative data sources
- **Negative controls strengthened findings**
  - Results clustered around the null effect of RR=1 (range 0.9–1.4)
  - Lower than rate ratios for GBS in both data sources
- **Evidence of more severe GBS (e.g., longer duration of hospitalization, higher percentage admitted to the ICU) among those ≥65 years**

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Thank You!

For more information, contact CDC
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