

# Post-Herpetic Neuralgia Occurrence and Herpes Zoster Recurrence in Immunocompromised Adults Aged 18 Years or Older in England: a Large Retrospective Cohort Study (Clinical Practice Research Datalink, 2012-2019)

Abda Mahmood<sup>1</sup>, Marie Nishimwe<sup>2</sup>, Yasmeeta Vekria<sup>3</sup>, Driss Oraichi<sup>4</sup>, Manjit Hunjan<sup>3</sup>, Saskia Hagenaars<sup>5</sup>, Karabo Keapoletswe<sup>6</sup>, Bhagya Chengat<sup>6</sup>, Spyros Paparrodopoulos<sup>7</sup>, Simeon Stavrev<sup>8</sup>, Sarah Lay-Flurrie<sup>6</sup>, Louise Raiteri<sup>6</sup>, Inga Posiuniene<sup>1</sup>, Susan Farrow<sup>3</sup>, Boriana Guimicheva<sup>3</sup> and Alen Marijam<sup>1</sup>

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## Background & Aim

- Herpes zoster (HZ), commonly known as shingles, is caused by reactivation of the varicella zoster virus and is common in immunocompromised (IC) individuals.<sup>1</sup>
- HZ may recur after the initial episode or result in complications, including post-herpetic neuralgia (PHN) that can persist for months or years after HZ.<sup>1</sup>

This study aims to provide robust, current data on **HZ complications** (including PHN) and **HZ recurrence** in IC adults.

## Study design

This retrospective cohort study analysed data from the Clinical Practice Research Datalink (CPRD) Aurum with linkage to Hospital Episode Statistics (HES) data and Office for National Statistics (ONS) data.

**Adults (≥18 years old)** with a CPRD-HES database record of any of the following IC conditions of interest (IC cohort) were identified from 2012–2018 and followed until 31 December 2019: haematological malignancies, haematopoietic stem cell transplantation, solid organ transplant, solid organ malignancies, human immunodeficiency virus, and autoimmune diseases.

Adults without any of the ICs of interest (IC-free cohort) were also identified and followed during the same period.

The proportion of adults who had PHN reported within 365 days following HZ diagnosis were estimated (two timepoint definitions: 0 to 365 and 90–365 days post-HZ event). Only HZ patients with 365 days of follow-up data were included in these analyses. HZ recurrence rates were estimated per 1,000 person-years (PYs) with 95% confidence intervals (CIs). Recurrent events were defined as HZ occurring after a 180-day HZ-free and HZ complications (except PHN) free period and included any HZ occurring after the first recurrent event.<sup>#</sup>

PHN and HZ Recurrence data were stratified by:

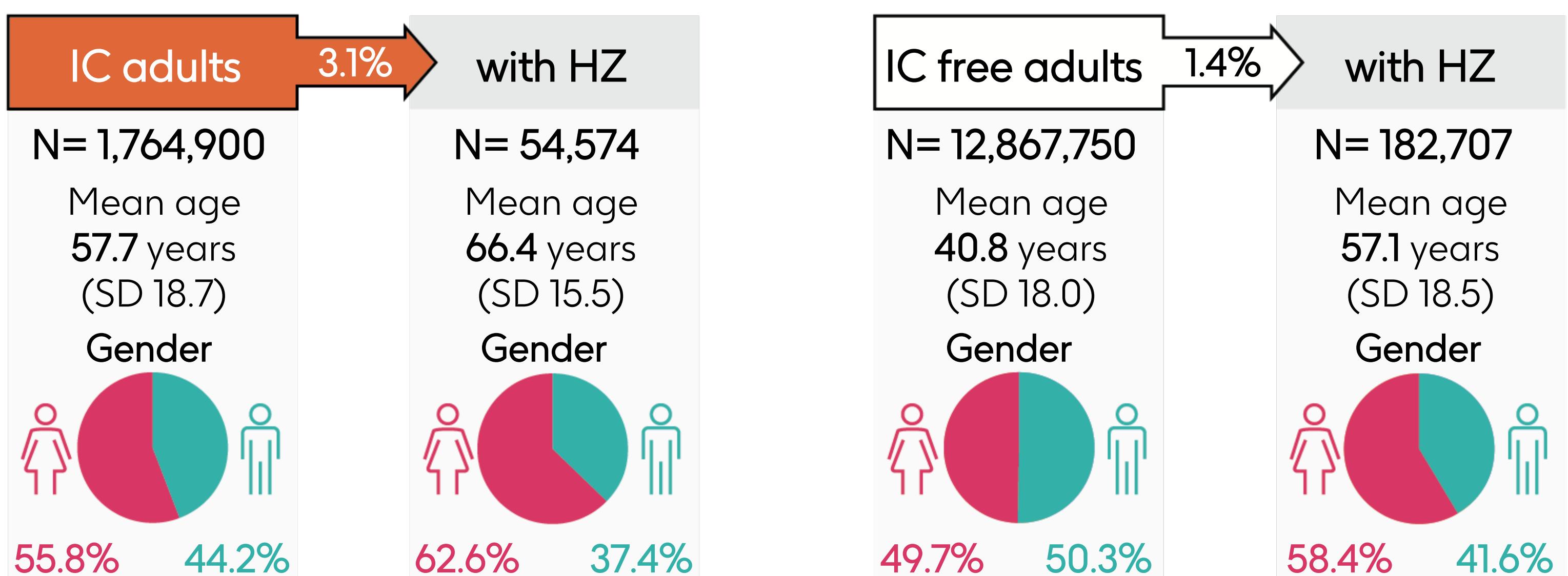
- Study population: IC cohort, IC-free cohort
- Age (years): 18–49, 50–59, 60–64, 65–69, 70–79, ≥80

<sup>#</sup>For complete definitions of HZ events, see supplementary table 1 (available through QR code)

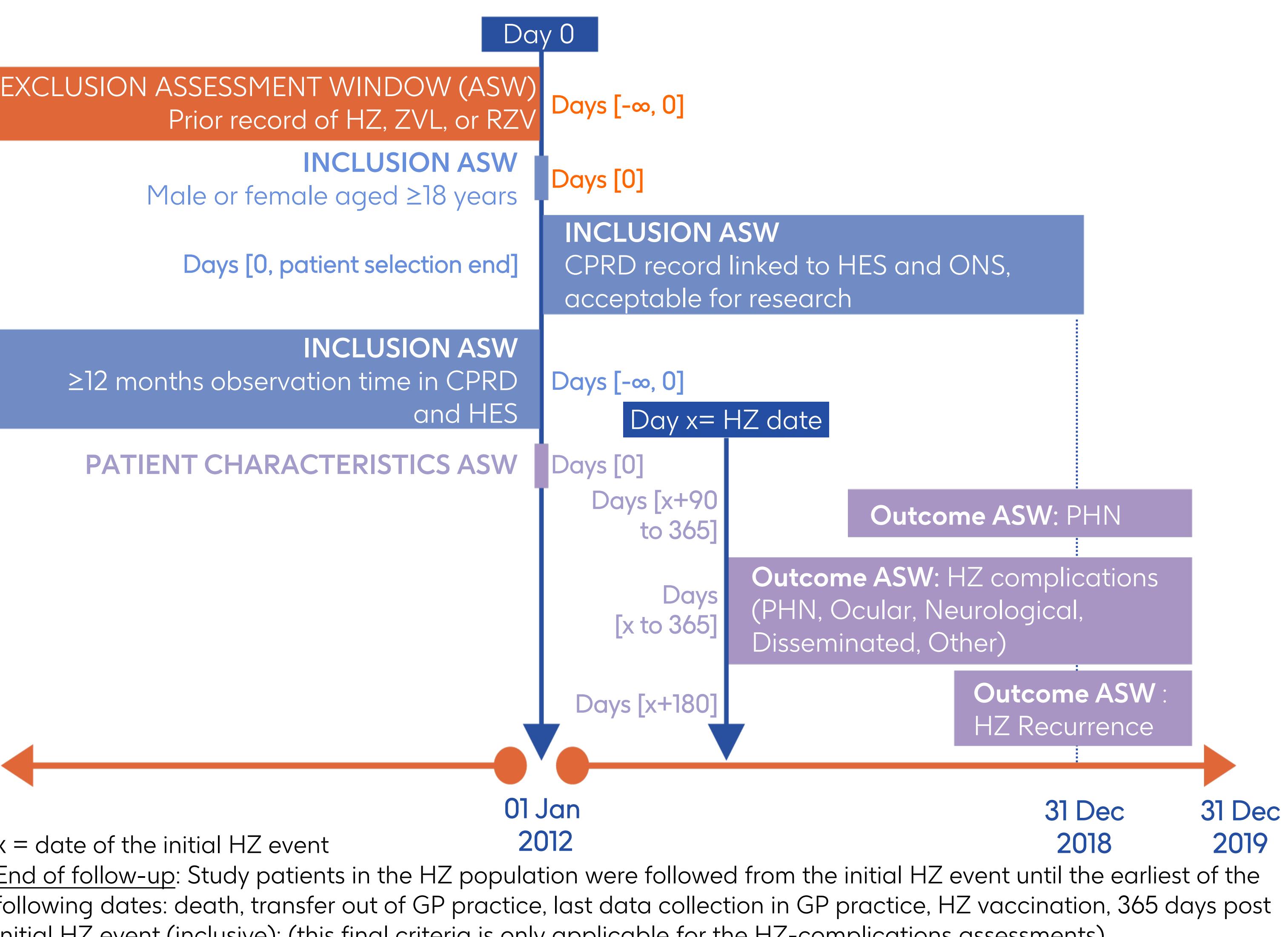
**Immunocompromised adults** with herpes zoster are at **higher risk** of developing **post-herpetic neuralgia** and **recurrent herpes zoster** compared to adults without the same immunocompromising conditions but with herpes zoster



## Demographics



**INDEX DATE**  
(latest of: study start date [01 Jan 2012], GP practice registration date, 18th birthday, or IC diagnosis)



## Results

Figure 1.

PHN cases reported between 90 to 365 days after HZ index date by age, in IC vs. IC-free adults\*

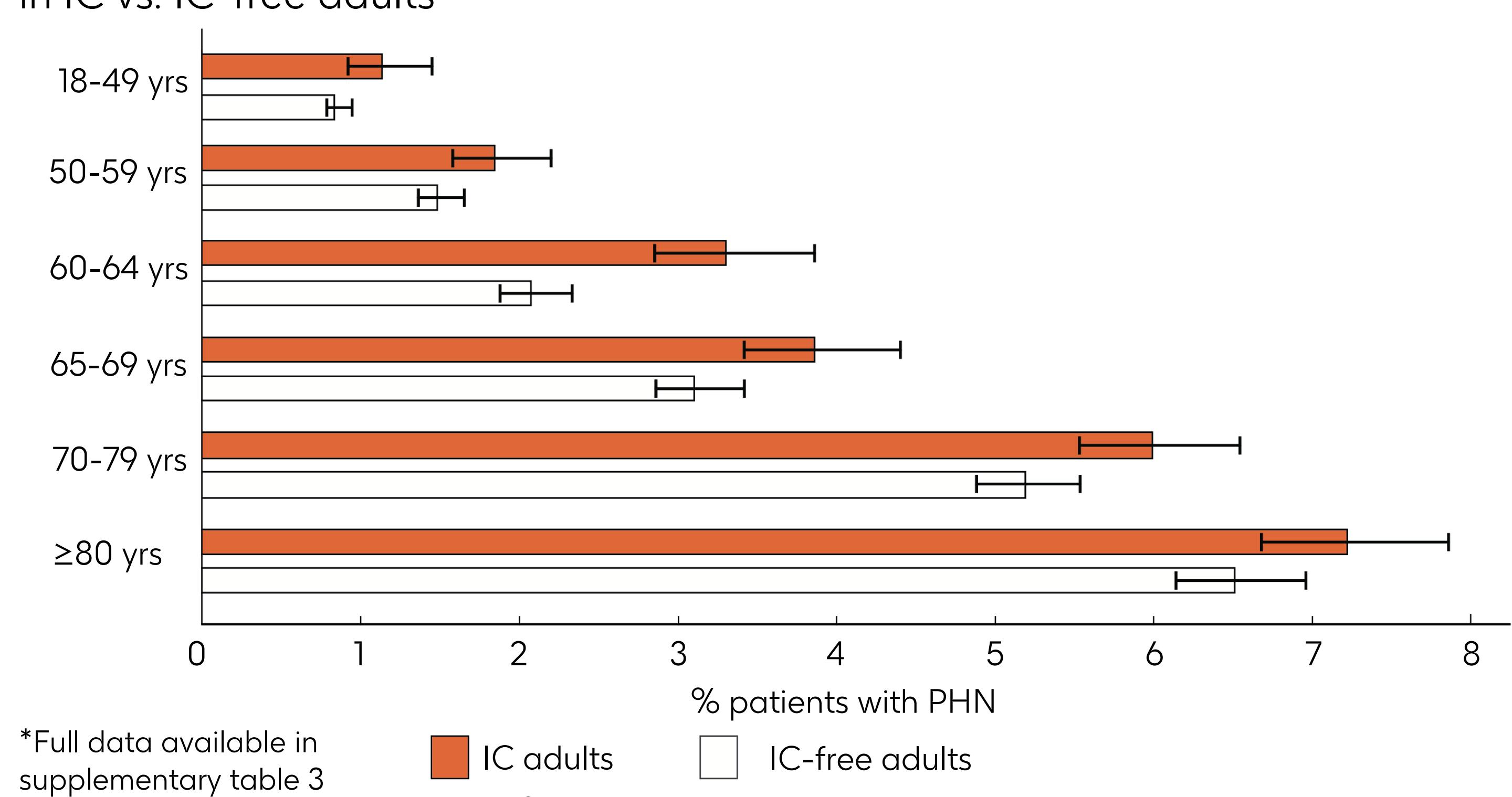


Figure 2.

PHN by age and timepoint post-HZ in IC adults\*

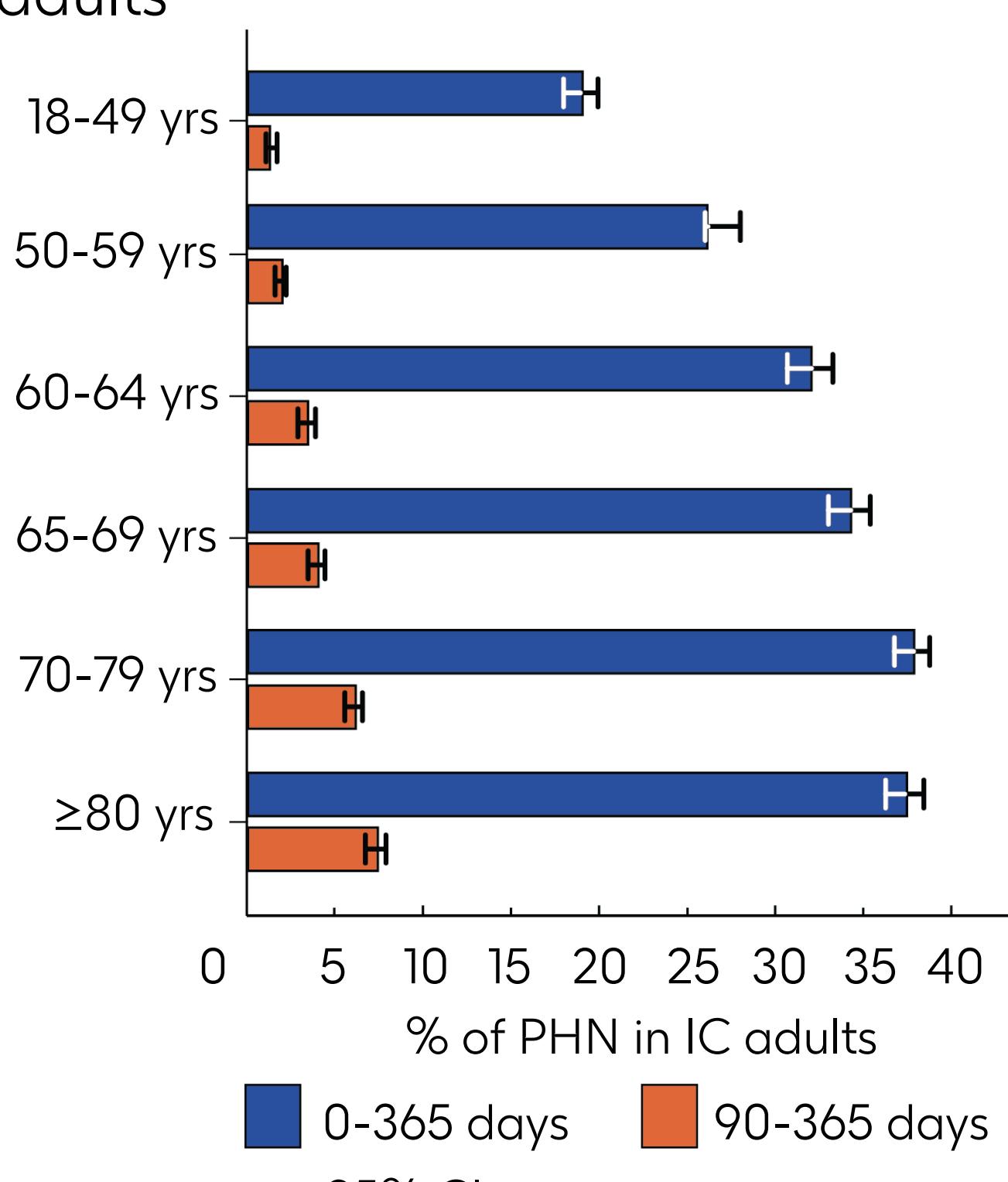
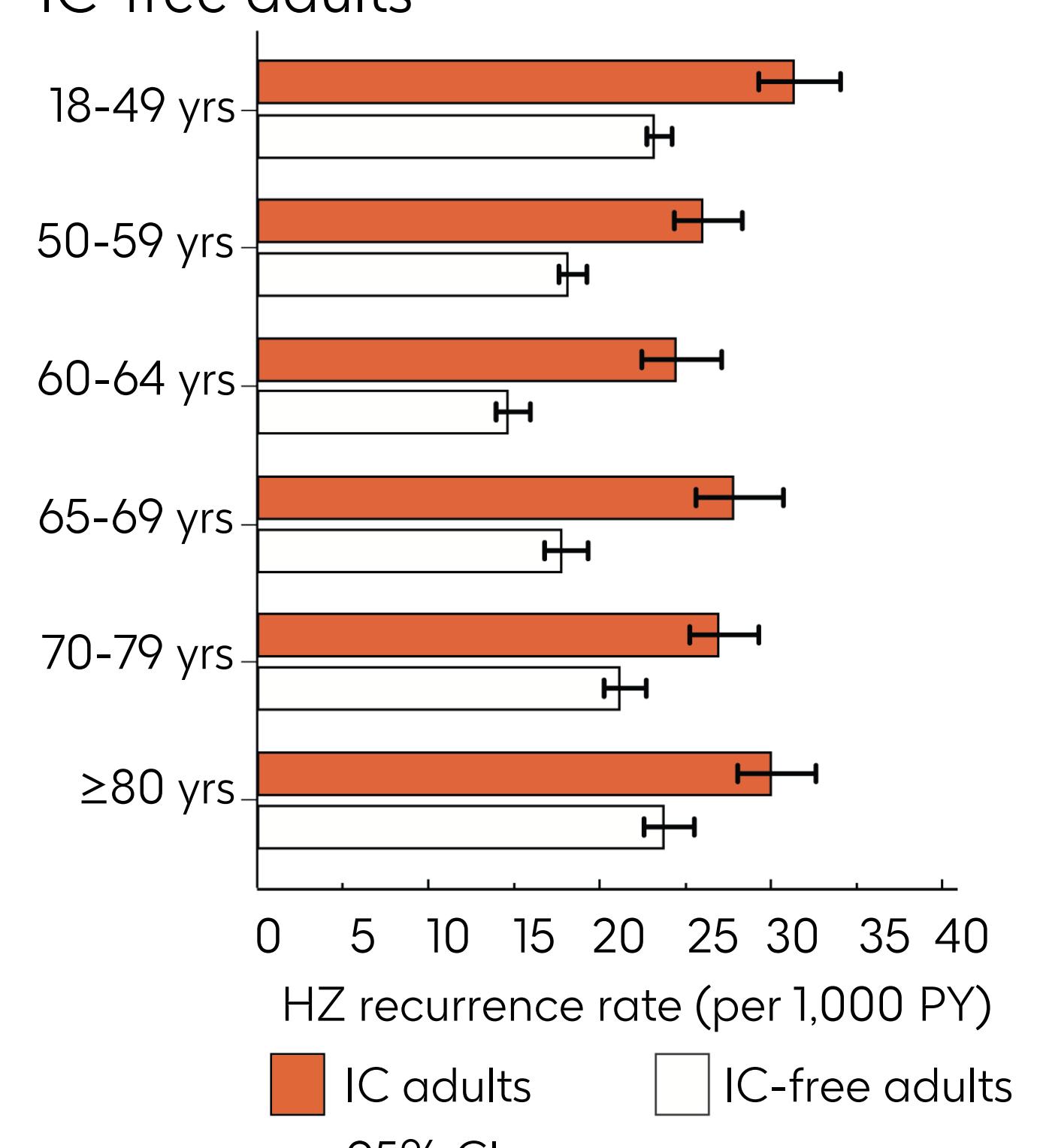


Figure 3.

HZ recurrence rates by age in IC vs. IC-free adults



## Conclusions



This large real-world study highlights that PHN and recurrent HZ are more common in IC than IC-free adults with HZ.



These findings could be used to advance HZ research and inform clinical guidelines and immunisation recommendations.

## Abbreviations

ASW: assessment window; CI: confidence interval; CPRD: Clinical Practice Research Datalink; GP: general practitioner; HES: Hospital Episode Statistics; HZ: herpes zoster; IC: immunocompromised; N: number; ONS: Office for National Statistics; PHN: post-herpetic neuralgia; PY: person-years; RZV: recombinant zoster vaccine; SD: standard deviation; vs.: versus; yrs: years; ZVL: zoster vaccine live

## References

1. Yanni EA, et al. Burden of herpes zoster in 16 selected immunocompromised populations in England: a cohort study in the Clinical Practice Research Datalink 2000–2012. *BMJ Open*. 2018;8(6):e020528.

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## Disclosures

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**Supplementary Table 1.** Herpes Zoster event definition

Variable used to define HZ	Description
HZ diagnosis	≥ 1 code for HZ (ICD-10 or MedCode from HES and CPRD) between the overall index date (exclusive) and 31 Dec 2019 (inclusive): <ul style="list-style-type: none"> <li>• HZ (including Not Otherwise Specified [NOS] or without complications)</li> <li>• Zoster without complications</li> <li>• Shingles</li> </ul>
PHN	1. Definite PHN: ≥ 1 code for PHN diagnosis (ICD-10 or MedCode from HES and CPRD) 90 to 365 days after the HZ index date (inclusive) which is identified between the overall index date (exclusive) and 31 Dec 2019 (inclusive) 2. Probable PHN defined as one of the below: <ol style="list-style-type: none"> <li>A second HZ code 90-365 days after the HZ index date (inclusive) with a same-day prescription of PHN medication (analgesic, antidepressant, or anticonvulsant)</li> <li>An unspecified neuralgia code 90 to 365 days after the HZ index date (inclusive)</li> <li>Zoster with other nervous system involvement 90 to 365 days after the HZ index date (inclusive)</li> </ol> For exploratory objectives (PHN within 365 days from HZ index date only), an expanded PHN definition was used that considered the entire 0 to 365 days after the HZ index date (inclusive)
Ocular complications	≥ 1 code for ocular complications (ICD-10 or MedCode from HES and CPRD), between the overall index date (exclusive) and 31 Dec 2019 (inclusive): <ul style="list-style-type: none"> <li>• HZ with ophthalmic complication</li> <li>• HZ with dermatitis of eyelid</li> <li>• HZ with keratoconjunctivitis</li> <li>• HZ iridocyclitis</li> <li>• Ophthalmic HZ infection</li> <li>• HZ ophthalmicus</li> <li>• Zoster ocular disease</li> </ul>
Neurological complications	≥ 1 code for neurological complications (ICD-10 or MedCode from HES and CPRD) between the overall index date (exclusive) and 31 Dec 2019 (inclusive): <ul style="list-style-type: none"> <li>• HZ with meningitis</li> <li>• HZ with other central nervous system (CNS) complication</li> <li>• Geniculate HZ</li> <li>• Ramsay - Hunt syndrome</li> <li>• Zoster encephalitis</li> <li>• Polyneuropathy in HZ</li> </ul>
Disseminated complications	≥ 1 code for disseminated complications (ICD-10 or MedCode from HES and CPRD), between the overall index date (exclusive) and 31 Dec 2019 (inclusive)
Other HZ complications	≥ 1 code for other HZ-related complications (ICD-10 or MedCode from HES and CPRD), between the overall index date (exclusive) and 31 Dec 2019 (inclusive): <ul style="list-style-type: none"> <li>• Dermatological complications (Hutchinson's sign)</li> <li>• Zoster with other complications</li> </ul>
HZ recurrent events	Any HZ event, in patients who have an HZ event, that is: <ul style="list-style-type: none"> <li>• Not the HZ index date of the patient;</li> <li>• Not a PHN event; and</li> <li>• For the first recurrence event: Occurs after a 180-day HZ-free and HZ complications free period (except PHN) from the HZ index date; or</li> <li>• For the second and subsequent recurrences: Occurs at any time after the previous HZ event</li> </ul>

## Abbreviations

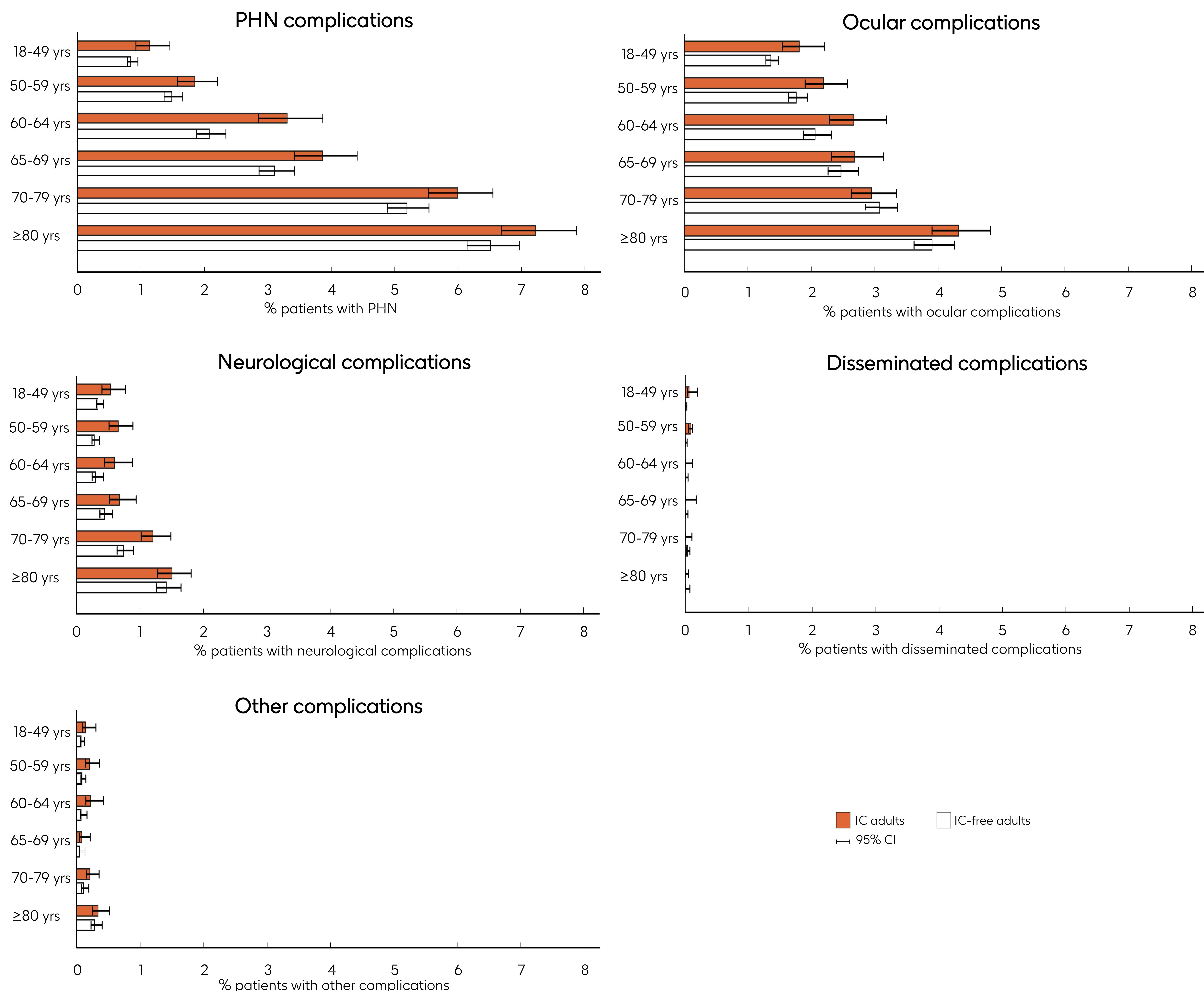
CNS: Central Nervous System; CPRD: Clinical Practice Research Datalink; HES: Hospital Episode Statistics; HZ: herpes zoster; ICD: International Classification of Diseases; NOS: Not Otherwise Specified; PHN: post-herpetic neuralgia

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Supplementary Figure 1. HZ complications per age group and IC condition



## Abbreviations

CI: confidence interval; HZ: herpes zoster; IC: immunocompromised; PHN: post-herpetic neuralgia; yrs: years

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Supplementary Table 2. Sociodemographic characteristics for HZ patients in IC and IC-free populations

Demographic characteristics	N	IC population with HZ		IC-free population with HZ	
		N	%	N	%
Age (years)	N	54,574	100.00%	182,707	100.00%
	Mean (SD)	66.41 (15.51)		57.12 (18.50)	
	Median (Q1-Q3)	67.76 (56.97-77.71)		58.59 (44.16-70.11)	
	Min-Max	18.00 - 105.40		18.00 - 109.08	
	Missing	0	0.00%	0	0.00%
Age group (years)	18-49	7,689	14.09%	60,121	32.91%
	50-59	9,188	16.84%	36,627	20.05%
	60-64	6,221	11.40%	19,343	10.59%
	65-69	7,897	14.47%	20,366	11.15%
	70-79	12,926	23.69%	26,548	14.53%
	≥80	10,653	19.52%	19,702	10.78%
	Missing/Unknown	0	0.00%	0	0.00%
Gender	Male	20,423	37.42%	75,979	41.59%
	Female	34,151	62.58%	106,728	58.41%
Practice region	North	15,157	27.77%	51,247	28.05%
	Midlands	11,196	20.52%	35,789	19.59%
	East	2,820	5.17%	9,201	5.04%
	South	18,730	34.32%	61,585	33.71%
	London	6,671	12.22%	24,885	13.62%
Ethnicity	Asian	1,645	3.01%	6,252	3.42%
	Black	699	1.28%	2,494	1.37%
	Mixed	193	0.35%	825	0.45%
	White	48,405	88.70%	136,280	74.59%
	Other	423	0.78%	2,084	1.14%
	Missing/Unknown	3,209	5.88%	34,772	19.03%

## Abbreviations

Hz: herpes zoster; IC: immunocompromised;  
Max: maximum; Min: minimum; N: number of patients; Q: quarter; SD: standard deviation

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Supplementary Table 2. Sociodemographic characteristics for HZ patients in IC and IC-free populations

Demographic characteristics	Cohort size	IC population with HZ		IC-free population with HZ	
		N	%	N	%
Smoking status	Current smoker	10,858	19.90%	39,834	21.80%
	Former smoker	25,081	45.96%	68,017	37.23%
	Non-smoker	15,964	29.25%	64,346	35.22%
	Missing/Unknown	2,671	4.89%	10,510	5.75%
Alcohol	Current drinker	46,358	84.95%	147,687	80.83%
	Ex-drinker	360	0.66%	966	0.53%
	Non-drinker	3,806	6.97%	11,181	6.12%
	Missing/Unknown	4,050	7.42%	22,873	12.52%
Socioeconomic status (patient-level)	Least deprived	13,179	24.15%	42,282	23.14%
	Less deprived	12,513	22.93%	40,956	22.42%
	Deprived	10,771	19.74%	36,263	19.85%
	More deprived	9,633	17.65%	33,523	18.35%
	Most deprived	8,417	15.42%	29,467	16.13%
	Missing/Unknown	61	0.11%	216	0.12%
Socioeconomic status (practice-level)	Least deprived	10,238	18.76%	33,432	18.30%
	Less deprived	9,807	17.97%	32,421	17.74%
	Deprived	12,042	22.07%	40,029	21.91%
	More deprived	11,143	20.42%	38,536	21.09%
	Most deprived	11,344	20.79%	38,289	20.96%
	Missing/Unknown	0	0.00%	0	0.00%
Follow-up period					
Time from relevant population index date until the end of follow-up (years)	N	54,574	100.00%	182,707	100.00%
	Mean (SD)	2.86 (2.16)		3.07 (2.21)	
	Median (Q1-Q3)	2.40 (1.01-4.41)		2.67 (1.17-4.74)	
	Min-Max	0.003 - 8.00		0.003 - 8.00	
	Missing	0	0.00%	0	0.00%

## Abbreviations

Hz: herpes zoster; IC: immunocompromised;  
Max: maximum; Min: minimum; N: number of patients; Q: quarter; SD: standard deviation

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Supplementary Table 3: Proportion of adults with HZ complications in the IC and IC-free populations, by age

Complication	IC			IC-free		
	N	n	% (95% CI)	N	n	% (95% CI)
<b>PHN (0–365 vs. 90–365 days post-HZ index)</b>						
<b>18-49 years</b>						
0–365	6,125	1,157	18.89 (17.93, 19.89)	48,291	6,804	14.09 (13.78, 14.40)
90–365	6,125	71	1.16 (0.92, 1.46)	48,291	413	0.86 (0.78, 0.94)
<b>50-59 years</b>						
0–365	7,385	1,991	26.96 (25.96, 27.98)	30,140	6,950	23.06 (22.59, 23.54)
90–365	7,385	138	1.87 (1.58, 2.20)	30,140	454	1.51 (1.37, 1.65)
<b>60-64 years</b>						
0–365	4,992	1,593	31.91 (30.63, 33.22)	15,934	4,695	29.47 (28.76, 30.18)
90–365	4,992	166	3.33 (2.86, 3.86)	15,934	334	2.10 (1.88, 2.33)
<b>65-69 years</b>						
0–365	6,129	2,093	34.15 (32.97, 35.35)	16,001	5,129	32.05 (31.34, 32.78)
90–365	6,129	239	3.90 (3.44, 4.41)	16,001	503	3.14 (2.88, 3.43)
<b>70-79 years</b>						
0–365	8,836	3,333	37.72 (36.72, 38.74)	18,288	6,402	35.01 (34.32, 35.70)
90–365	8,836	532	6.02 (5.54, 6.54)	18,288	954	5.22 (4.90, 5.55)
<b>≥80 years</b>						
0–365	7,572	2,824	37.30 (36.21, 38.39)	14,222	4,972	34.96 (34.18, 35.75)
90–365	7,572	550	7.26 (6.70, 7.87)	14,222	932	6.55 (6.16, 6.97)

## Abbreviations

CI: confidence interval; HZ: herpes zoster;  
 IC: immunocompromised; N: number of patients with HZ and at least 365 days of follow up;  
 n: number of the patients with HZ with this complication; PHN: post-herpetic neuralgia

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Complication	IC			IC-free		
	N	n	% (95% CI)	N	n	% (95% CI)
<b>Neurological (0–365 days post-HZ index)</b>						
18–49 years	6,125	34	0.56 (0.40, 0.77)	48,291	175	0.36 (0.31, 0.42)
50–59 years	7,385	50	0.68 (0.51, 0.89)	30,140	89	0.30 (0.24, 0.36)
60–64 years	4,992	31	0.62 (0.44, 0.88)	15,934	51	0.32 (0.24, 0.42)
65–69 years	6,129	43	0.70 (0.52, 0.94)	16,001	73	0.46 (0.36, 0.57)
70–79 years	8,836	109	1.23 (1.02, 1.49)	18,288	139	0.76 (0.64, 0.90)
≥80 years	7,572	116	1.53 (1.28, 1.83)	14,222	205	1.44 (1.26, 1.65)
<b>Ocular (0–365 days post-HZ index)</b>						
18–49 years	6,125	113	1.84 (1.54, 2.21)	48,291	669	1.39 (1.28, 1.49)
50–59 years	7,385	164	2.22 (1.91, 2.58)	30,140	538	1.79 (1.64, 1.94)
60–64 years	4,992	135	2.70 (2.29, 3.19)	15,934	333	2.09 (1.88, 2.32)
65–69 years	6,129	166	2.71 (2.33, 3.15)	16,001	400	2.50 (2.27, 2.75)
70–79 years	8,836	263	2.98 (2.64, 3.35)	18,288	568	3.11 (2.86, 3.37)
≥80 years	7,572	330	4.36 (3.92, 4.84)	14,222	560	3.94 (3.63, 4.27)
<b>Disseminated (0–365 days post-HZ index)</b>						
18–49 years	6,125	5	0.08 (0.03, 0.19)	48,291	*	* (0.00, 0.02)
50–59 years	7,385	8	0.11 (0.05, 0.21)	30,140	*	* (0.00, 0.02)
60–64 years	4,992	*	* (0.00, 0.11)	15,934	*	* (0.00, 0.04)
65–69 years	6,129	*	* (0.03, 0.17)	16,001	*	* (0.00, 0.04)
70–79 years	8,836	*	* (0.01, 0.10)	18,288	6	0.03 (0.02, 0.07)
≥80 years	7,572	0	0.00 (0.00, 0.05)	14,222	*	* (0.01, 0.07)
<b>Other HZ complications (0–365 days post-HZ index)</b>						
18–49 years	6,125	10	0.16 (0.09, 0.30)	48,291	45	0.09 (0.07, 0.12)
50–59 years	7,385	16	0.22 (0.13, 0.35)	30,140	29	0.10 (0.07, 0.14)
60–64 years	4,992	12	0.24 (0.14, 0.42)	15,934	15	0.09 (0.06, 0.16)
65–69 years	6,129	6	0.10 (0.04, 0.21)	16,001	12	0.07 (0.04, 0.13)
70–79 years	8,836	20	0.23 (0.15, 0.35)	18,288	23	0.13 (0.08, 0.19)
≥80 years	7,572	27	0.36 (0.25, 0.52)	14,222	42	0.30 (0.22, 0.40)

## Abbreviations

CI: confidence interval; HZ: herpes zoster;  
IC: immunocompromised; N: number of patients with HZ and at least 365 days of follow up; n: number of the patients with HZ with this complication

# Post-Herpetic Neuralgia Occurrence and Herpes Zoster Recurrence in Immunocompromised Adults Aged 18 Years or Older in England: a Large Retrospective Cohort Study (Clinical Practice Research Datalink, 2012-2019)

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Supplementary Table 4: Proportion of adults with HZ recurrence in the IC and IC-free populations, by age

	IC		IC-free	
	N	Rate/1,000 PY (95% CI)	N	Rate/1,000 PY (95% CI)
18–49 years	678	31.58 (29.25, 34.02)	3,936	23.43 (22.70, 24.17)
50–59 years	679	26.26 (24.32, 28.29)	1,987	18.39 (17.59, 19.22)
60–64 years	432	24.68 (22.41, 27.09)	846	14.89 (13.90, 15.92)
65–69 years	472	28.06 (25.59, 30.68)	783	18.00 (16.76, 19.29)
70–79 years	710	27.19 (25.22, 29.24)	1,167	21.41 (20.20, 22.67)
≥80 years	685	30.25 (28.03, 32.58)	1,052	23.99 (22.56, 25.48)

## Conflicts of interest

AbM, MN, YV, DO, CO, IP, SF, BG, and AIM are GSK employees. AbM, AIM, MN and DO hold financial equities in GSK. AbM declares being a member of the board of trustees for a mental health charity, Beyond Conflict (registered charity number: 1176499) – voluntary (unpaid). YV, MH, IP holds financial equities in GSK and Haleon and travel support from GSK. MH was a GSK employee during study conception, design and execution. SF holds financial equities in GSK and Sanofi and Organon. CO holds financial equities in GSK and Pfizer. BG holds financial equities in GSK and MSD. SH, KK, BC, SP, LR, SS, SL-F are IQVIA Ltd. employees. IQVIA received financial compensation from GSK for protocol development, analysis and conduct of the present study. These authors declare no other financial and non-financial relationships and activities.

## Abbreviations

CI: confidence interval; HZ: herpes zoster;  
IC: immunocompromised; N: number of  
HZ recurrences; PY: person-years