

EVALUATION OF SHINGRIX VACCINE AGAINST HERPES ZOSTER

SUPPLEMENT



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Reported interests:

All experts and stakeholders consulted within this report were selected because of their involvement in the topic of Herpes Zoster. Therefore, by definition, each of them might have a certain degree of conflict of interest to the main topic of this report.

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- **The external experts were consulted about a (preliminary) version of the scientific report. Their comments were discussed during meetings. They did not co-author the scientific report and did not necessarily agree with its content.**
- **Subsequently, a (final) version was submitted to the validators. The validation of the report results from a consensus or a voting process between the validators. The validators did not co-author the scientific report and did not necessarily all three agree with its content.**
- **Finally, this report has been approved by common assent by the Executive Board.**
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APPENDIX 1. BURDEN OF DISEASE

Appendix 1.1. Search string for retrieval of systematic reviews

Search string MEDLINE on 16/09/2022

1. herpes zoster[MeSH]	12 897
2. burden OR epidemiology OR frequen* OR inciden* OR complicat* OR neuralgia OR cardi* OR cerebrovascular OR stroke OR ophtalm* OR disseminat* OR immune* OR hospital* OR mortality OR lethality OR death	14 824 407
3. 1 AND 2	9229
4. study type: systematic review	97

Inclusion criteria:

1. Report on incidence, clinical complications, hospitalization or death of herpes zoster
2. Include any type of studies
3. Studies in Western countries

Exclusion criteria:

4. Focused on a specific country
5. Focused on treatment of zona

Appendix 1.2. Search string for retrieval of primary studies

Search string MEDLINE on 15/07/2019

1. herpes zoster[MeSH]	11 469
2. burden OR epidemiology OR frequen* OR inciden* OR complicat* OR neuralgia OR cardi* OR cerebrovascular OR stroke OR ophtalm* OR disseminat* OR immune* OR hospital* OR mortality OR lethality OR death	10 817 730
3. 1 AND 2	1356
4. UK OR England OR scotland OR ireland OR france OR germany OR netherlands OR belgium OR spain OR italy OR norway OR denmark OR sweden OR finland OR austria OR switzerland OR portugal	56 896
5. 3 AND 4 with time limit: 2013/12/01 to 2019/07/15	374

Inclusion criteria:

1. Report on incidence, clinical complications, hospitalization or death of herpes zoster at the community level
2. Any types of study
3. Include >400 cases of zona

Exclusion criteria:

4. Focused on treatment of zona
5. Self-reports of physician-diagnosed zoster
6. A specific sub-group of patients only
7. Cost-effectiveness studies with data derived from the literature
8. Case reports
9. Systematic reviews



The search was carried out in MEDLINE on 15/07/2019. Our research project was put on hold between September 2019 and December 2021 because availability of Shingrix for the Belgian market was reduced. When we restarted the research in early 2022, no attempt was made to update our pragmatic review as we considered unlikely that new contradictory evidence would emerge on incidence, risk factors and complications of HZ. However, the content of more recent studies included in recent systematic literature review was screened and relevant information was extracted.

We retrieved 374 hits. Three other references were found by screening paper bibliography (Yanni 2018,¹ Munoz 2018,² De Boer et al. 2018³). Three additional studies were retrieved by searching grey literature.⁴⁻⁷ Therefore, we screened in total 380 references. 327 studies were excluded on title and/or abstract. Therefore, 53 studies were screened in full, among which 31 were retained and 21 were excluded. List of excluded studies (with reasons for exclusion) can be found in Table 1.

Table 1 – Population-based studies excluded and reasons for exclusion

Reason for exclusion	Studies
Too small sample	1. Amicizia 2017 ⁸ 2. Matthews 2018 ⁹
Methods	1. Belchior 2016 ¹⁰ (data from Van Hoek 2009 ¹¹ and Chiappe ¹² are used) 2. Blank 2017 ¹³ (data collection for incidence not described; results for PHN from Gauthier 2009 ¹⁴) 3. Breuer 2014 ¹⁵ (already included in review by Forbes ¹⁶) (already included in review by Forbes ¹⁶) 4. Caputo 2019 ¹⁷ (self-reports of physician-diagnosed HZ) 5. Curran 2017 ¹⁸ (results are from Hillebrand 2015 ¹⁹) 6. Langan 2014 ²⁰ 7. Salleras 2015 ²¹ (incidence based on extrapolation of results from 1 city) 8. Schmidt 2017 ²² (computation based only on prescription of antiviral drugs) 9. Studahl 2013 ²³ (already included in review by Kaway) 10. Sundstrom 2015 ²⁴ (already included in review by Forbes ¹⁶) 11. Ultsch 2013 ²⁵ (already included in review by Kaway; no incidence of hospitalization) 12. Van Wijck ²⁶ (patient data were collected via a web-based questionnaire) 13. Wemer 2017 ^{27, 28} (guidelines) 14. Zorzoli 2018 ²⁹ (narrative review)
Out of Europe	1. Curran 2018 ³⁰ 2. Curran 2018 ³¹
Other outcomes	1. Blein 2015 ³² (no incidence figures on hospitalization) 2. Boccalini 2017 ³³ 3. Horn 2016 ³⁴ (no incidence figures)



Appendix 1.3. Proportion of HZ patients receiving a treatment in Sciensano, GP sentinel network

Table 2 – Number of reported antiviral treatment for herpes zoster infection, by age-group and sex, 2006-2012

Sex	Age group (in years)	Treatment						Total	
		Yes		No		Unknown			
		n	%	n	%	n	%	n	%
Male	0–9	36	34.3%	66	62.9%	3	2.9%		
	10–19	92	48.4%	98	51.6%	0	0.0%		
	20–29	93	68.9%	42	31.1%	0	0.0%		
	30–39	104	67.1%	50	32.3%	1	0.6%		
	40–49	157	75.5%	51	24.5%	0	0.0%		
	50–59	226	78.5%	61	21.2%	1	0.3%		
	60–69	249	79.0%	65	20.6%	1	0.3%		
	70–79	302	86.3%	47	13.4%	1	0.3%		
	80–89	144	75.8%	45	23.7%	1	0.5%		
	90+	21	100.0%	0	0.0%	0	0.0%		
	Unknown	30	75.0%	10	25.0%	0	0.0%		
Total in Male		1454	72.8%	535	26.8%	8	0.4%	1997	41.2%
Female	0–9	37	30.1%	86	69.9%	0	0.0%		
	10–19	83	46.9%	90	50.8%	4	2.3%		
	20–29	89	60.5%	57	38.8%	1	0.7%		
	30–39	101	67.8%	46	30.9%	2	1.3%		
	40–49	203	76.3%	62	23.3%	1	0.4%		
	50–59	339	77.0%	99	22.5%	2	0.5%		
	60–69	364	82.2%	75	16.9%	4	0.9%		
	70–79	431	82.4%	89	17.0%	3	0.6%		
	80–89	340	82.7%	66	16.1%	5	1.2%		
	90+	58	78.4%	15	20.3%	1	1.4%		
	Unknown	32	69.6%	14	30.4%	0	0.0%		
Total in Female		2077	74.2%	699	25.0%	23	0.8%	2799	57.8%
Unknown	0–9	1	50.0%	1	50.0%	0	0.0%		
	10–19	2	66.7%	0	0.0%	1	33.3%		
	20–29	1	33.3%	0	0.0%	2	66.7%		
	30–39	0	0.0%	0	0.0%	0	0.0%		
	40–49	1	12.5%	1	12.5%	6	75.0%		
	50–59	0	0.0%	1	14.3%	6	85.7%		



60–69	3	27.3%	2	18.2%	6	54.5%	
70–79	3	50.0%	0	0.0%	3	50.0%	
80–89	2	50.0%	1	25.0%	1	25.0%	
90+	1	100.0%	0	0.0%	0	0.0%	
Unknown	1	50.0%	0	0.0%	1	50.0%	
Total unknown	15	31.9%	6	12.8%	26	55.3%	47 1.0%
Total	3546	73.2%	1240	25.6%	57	1.2%	4843

Data source: Sciensano, GP sentinel network

Table 3 – Number of reported antiviral treatment for herpes zoster or PHN infection, by age-group and sex, 2021

Sex	Age group (in years)	Only 2021 (shingles and PHN, N=194)			
		n	%	n	%
Female		Yes		No	
	0–4	0	0%	0	0%
	5–14	0	0%	2	100%
	15–19	0	0%	0	0%
	20–29	7	77.8%	2	22.2%
	30–49	14	58.3%	10	41.7%
	50–59	27	93.1%	2	6.9%
	60–74	20	71.4%	8	28.6%
	>=75	20	60.6%	13	39.4%
	Total	88	70.4%	37	29.6%
Male		Yes		No	
	0–4	0	0%	0	0%
	5–14	3	42.9%	4	57.1%
	15–19	0	0%	0	0%
	20–29	8	100%	0	0%
	30–49	5	71.4%	2	28.6%
	50–59	6	66.7%	3	33.3%
	60–74	9	45%	11	55%
	>=75	14	77.8%	4	22.2%
	Total	45	65.2%	24	34.8%

Data source: Sciensano, GP sentinel network



Appendix 1.4. Hospitalisation rate in Sciensano, GP sentinel network

Table 4 – Number of reported hospitalisations for herpes zoster infection, 2010-2012

Sex	Age (in years)	Hospitalisation						Total	
		Yes n	%	No n	%	Unknown n	%		
Male	0–9	0	0.0%	42	100.0%	0	0.0%		
	10–19	1	1.4%	72	98.6%	1	1.4%		
	20–29	0	0.0%	56	100.0%	0	0.0%		
	30–39	1	2.0%	50	98.0%	0	0.0%		
	40–49	0	0.0%	84	100.0%	1	1.2%		
	50–59	0	0.0%	127	100.0%	0	0.0%		
	60–69	1	0.8%	122	99.2%	1	0.8%		
	70–79	2	1.4%	136	98.6%	3	2.1%		
	80–89	3	3.5%	82	95.3%	1	1.2%		
	90+	1	12.5%	7	87.5%	0	0.0%		
	Unknown	0	0.0%	7	100.0%	1	12.5%		
Total in Male		9	1.1%	785	98.7%	8	1.0%	802	41.5%
Female	0–9	1	2.0%	50	98.0%	0	0.0%		
	10–19	0	0.0%	76	100.0%	1	1.3%		
	20–29	2	3.7%	52	96.3%	0	0.0%		
	30–39	0	0.0%	77	100.0%	1	1.3%		
	40–49	2	1.8%	107	98.2%	0	0.0%		
	50–59	5	2.9%	165	95.9%	4	2.3%		
	60–69	3	1.8%	165	98.2%	1	0.6%		
	70–79	7	3.5%	192	96.0%	1	0.5%		
	80–89	2	1.4%	140	97.9%	1	0.7%		
	90+	0	0.0%	29	100.0%	1	3.3%		
	Unknown	0	0.0%	13	100.0%	0	0.0%		
Total in Female		22	2.0%	1066	97.6%	10	0.9%	1098	56.9%
Unknown	0–9	0	0.0%	1	100.0%	0	0.0%		
	10–19	0	0.0%	0	0.0%	1	0.0%		
	20–29	0	0.0%	1	100.0%	2	66.7%		
	30–39	0	0.0%	0	0.0%	0	0.0%		
	40–49	0	0.0%	1	100.0%	6	85.7%		



50–59	0	0.0%	0	0.0%	5	0.0%	
60–69	0	0.0%	1	100.0%	4	80.0%	
70–79	0	0.0%	1	100.0%	3	75.0%	
80–89	0	0.0%	2	100.0%	1	33.3%	
90+	0	0.0%	0	0.0%	1	0.0%	
Unknown	0	0.0%	0	0.0%	1	0.0%	
Total in Unknown	0	0.0%	7	100.0%	24	77.4%	31 1.6%
TOTAL	31	1.6%	1858	98.1%	42	2.2%	1931

Data source: Sciensano, GP sentinel network



Appendix 1.5. Use of antivirals in the permanent sample

Appendix 1.5.1. Acyclovir

In 2012 in the ambulatory sector, 38 340 boxes of acyclovir were bought by 11 280 patients which corresponds to a ratio box/patient of 3.4. The majority of the acyclovir boxes purchased (86.6%) were of 800 mg*35 units in both age-groups (see Table 5).

Table 5 – Number of acyclovir boxes bought, by conditioning, by age-group, 2012

	< 65 years (%)	≥65 years (%)	Total (%)
Acyclovir 200 mg * 25	1 840 (7.6)	640 (4.6)	2660 (6.9)
Acyclovir 400 mg * 20	2 000 (8.2)	660 (4.7)	2480 (6.5)
Acyclovir 800 mg * 35	20 440 (84.2)	12 760 (90.8)	33 200 (86.6)
Total	24 280 (100)	14 060 (100)	38 340 (100)

Data source: IMA – AIM, permanent sample (PS), N= 11 280 patients (N <65 years=7160; N ≥65 years=4120)

Total number of defined daily dose (DDD)^a for acyclovir equals to 240 820, the largest amount of DDD is attributed to acyclovir 800 mg*35 and the distribution of DDD across acyclovir conditioning did not vary between age-groups (see Table 6).

^a Defined daily dose (DDD) is the assumed average maintenance dose per day for a drug used for its main indication in adults. DDDs are standardized doses provided as part of the Anatomical Therapeutic Chemical drug classification system maintained by the WHO Collaborating Centre for Drug Statistics Methodology (www.whocc.no/atcddd). The DDD is an internationally accepted unit for measuring medicine use and for making comparisons between countries

Table 6 – Number of acyclovir DDD bought, by conditioning, 2012

Conditioning	< 65 years	≥65 years	Total
Acyclovir 200 mg * 25	2300	800	3100
Acyclovir 400 mg * 20	4000	1320	5320
Acyclovir 800 mg * 35	143 080	89 320	232 400
Total	149 380	91 440	240 820

Data source: IMA – AIM, permanent sample (PS)

Among patients who bought acyclovir 800 mg*35 units (n=9 900), majority bought one box (n= 4 720, 47.7%) but a significant proportion also bought between 4 and 10 boxes (28.3%). Distribution of the number of acyclovir boxes by conditioning was similar between age-groups (see Table 7).

**Table 7 – Number of patients who bought acyclovir, by conditioning, by age-group, 2012**

Number of boxes	<65 years (n=7160)			≥65 years (n=4120)			Total (n=11 280)		
	Aci20 N patients (%)	Aci25 N patients (%)	Aci35 N patients (%)	Aci25 N patients (%)	Aci20 N patients (%)	Aci35 N patients (%)	Aci20 N patients (%)	Aci25 N patients (%)	Aci35 N patients (%)
1	240 (50.0)	600 (68.2)	2 640 (44.0)	140 (63.6)	60 (50.0)	2 080 (53.3)	300 (50.0)	740 (67.3)	4720* (47.7)
2	40 (8.3)	40 (4.5)	680 (11.3)	0 (0.0)	20 (16.7)	400 (10.3)	60 (10.0)	40 (3.6)	1080 (10.9)
3	0 (0.0)	80 (9.1)	480 (8.0)	20 (9.1)	20 (16.7)	300 (7.7)	20 (3.3)	100 (9.1)	780 (7.9)
4 to 10	120 (25.0)	160 (18.2)	1 880 (31.3)	60 (27.3)	0 (0.0)	920 (23.6)	120 (20.0)	220 (20.0)	2800 (28.3)
>10	80 (16.7)	0 (0.0)	320 (5.3)	0 (0.0)	20 (16.7)	200 (5.1)	100 (16.7)	0 (0.0)	520 (5.3)
Total*	480 (100)	880 (100)	6 000 (100)	220 (100)	120 (100)	3 900 (100)	600 (100)	1100 (100)	9900 (100)

* N = 11 280 patients, some patients bought multiple type of acyclovir box, data source: IMA – AIM, permanent sample (PS), Aci20= Acyclovir 400 mg * 20, Aci25= Acyclovir 200 mg * 25, Aci35= Acyclovir 800 mg * 35, * Expected posology for HZ infection.

Among patients who bought acyclovir35*800 mg, 4.2% (420/9900) bought it chronically – i.e. at least five purchases with less than 32 days between each (see Table 8).

Table 8 – Number of patients with chronic purchase of acyclovir35*800 mg, by age-group, 2012

	<65 years (n= 2000)	≥65 years (n= 1460)	Total (n= 3460)
Chronic purchase Aci35*800 mg (2-4 times*)	1760	1280	3 040
Chronic purchase Aci35*800 mg (5 times**)	80	100	180
Chronic purchase Aci35*800mg (>5 times***)	160	80	240

* Two to four Aci35 purchases with less than 32 days between each, ** Five Aci35 purchases with less than 32 days between each, *** More than five Aci35 purchases with less than 32 days between each.

Among patients who bought acyclovir (n= 11 280), 50% purchased more than 7.25 Defined Daily Dose (DDD) (P25:7-P75:28 DDD) (see Table 9, Figure 1). Average DDD is higher in older patients but variation of DDD is higher in younger patients (see Table 9).

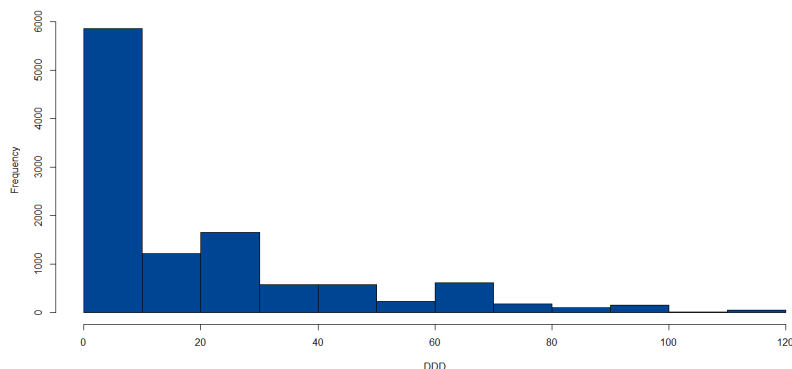
Table 9 – Average and median DDD acyclovir purchased, by age-group, 2012

DDD Acyclovir	<65 years (n= 7160)	≥65 years (n= 4120)	Total (n=11 280)
DDD Mean (SD)	20.86 (21.65)	22.19 (24.93)	21.35 (22.88)
DDD Median (P25-P75)	8.25 (7-28)	7 (7-28)	7.25 (7-28)

Data source: IMA – AIM, permanent sample (PS), SD=Standard Deviation, P25=25th percentile, P75=75th percentile



Figure 1 – Distribution of acyclovir DDD, 2012



Data source: IMA – AIM, permanent sample (PS)

Appendix 1.5.2. Valacyclovir

In 2012 in the ambulatory sector, 1140 patients (<65 years: 680 patients; >65 years: 460 patients) bought 3000 boxes of valacyclovir (500 mg * 42 units or 500 mg*10) and 53.3% have been bought by young patient (<65 years) (see Table 10).

Table 10 – Number of valacyclovir boxes bought, by conditioning, by age-group, 2012

	< 65years (%) (n=680)	≥65 years (%) (n=460)	Total (%)
Valacyclovir 500 mg * 10	880 (55.0)	320 (22.9)	1200 (40.0)
Valacyclovir 500 mg * 42	720 (45.0)	1080 (77.1)	1800 (60.0)
Total	1600 (100)	1400 (100)	3000 (100)

Data source: IMA – AIM, permanent sample (PS), n=1140 patients

Table 11 – Number of valacyclovir DDD bought, by conditioning, 2012

	<65 years	≥65 years	Total
Valacyclovir 500 mg * 10	6160	2240	8400
Valacyclovir 500 mg * 42	5040	7560	12 600
Total	11 200	9800	21 000

Data source: IMA – AIM, permanent sample (PS), n=1140 patients

**Table 12 – Number of valacyclovir box bought, by conditioning, by age-group, 2012**

Number of boxes	<65 years vala10 N patient (%)	<65 years vala42 N patient (%)	≥65 years vala10 N patient (%)	≥65 years vala42 N patient (%)	Total Vala42 N patient (%)	Total Vala10 N patient (%)
1	240 (66.7)	200 (62.5)	120 (66.7)	220 (65.7)	440 (64.7)	360 (66.7)
2	80 (22.2)	0 (0.0)	20 (11.1)	0 (0.0)	0 (0.0)	100 (18.5)
3	0 (0.0)	80 (25.0)	0 (0.0)	20 (5.9)	100 (14.7)	0 (0.0)
4 to 10	0 (0.0)	40 (12.5)	40 (22.2)	80 (23.5)	120 (17.6)	40 (7.4)
>10	40 (0.0)	0 (0.0)	0 (0.0)	20 (5.9)	20 (2.9)	40 (7.4)
Total*	360 (100)	320 (100)	180 (100)	340 (100)	680 (100)	540 (100)

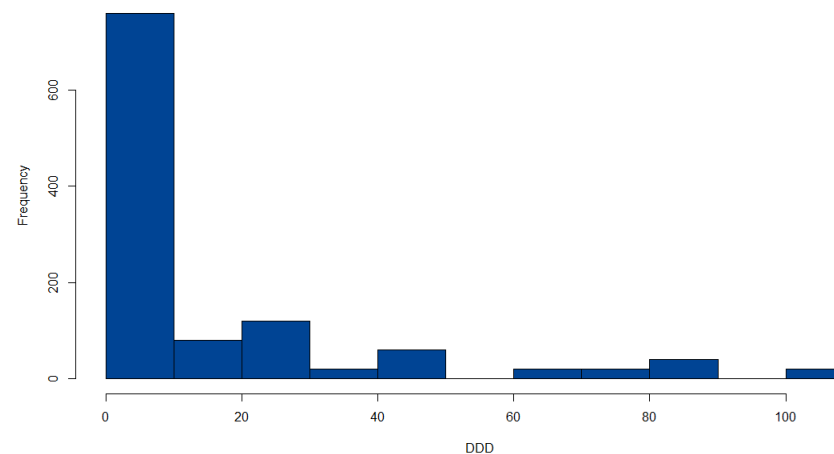
Data source: IMA – AIM, permanent sample (PS), vala10 = 10*500 mg, vala42 = 42*500 mg, * N = 1140 patients, some patients bought multiple type of valacyclovir box.

Half of the patients bought more than 7 DDD (P25:7-P75:16.63:105 DDD) and median DDD was equivalent between age-groups (see Table 13 & Figure 2).

Table 13 – Average and median DDD valacyclovir bought, by age-group, 2012

DDD valacyclovir	< 65 years (n= 680)	≥65 years (n= 460)	Total (n=1140)
DDD Mean (SD)	16.5 (20.4)	21.3 (27.6)	18.4 (23.4)
DDD Median (P25-P75)	7 (7-14)	7 (7-21)	7 (7-16.6)

Data source: IMA – AIM, permanent sample (PS)

Figure 2 – Distribution of the DDD of valacyclovir bought in 2012

Data source: IMA – AIM, permanent sample (PS)



Appendix 1.6. Hospitalisations with HZ as primary and secondary diagnosis

Table 14 – Proportion of patients with HZ as primary, secondary, primary and secondary diagnosis, by type of stay, 2008-2016

Diagnosis	2008		2009		2010		2011		2012		2013		2014		2016	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Inpatient																
Primary	1 192	47.6	1 116	44.6	1 014	42.3	955	40.1	1 005	41.1	956	39.4	980	39.1	934	35.2
Secondary	1 231	49.1	1 319	52.6	1 316	54.9	1 357	57.0	1 363	55.8	1 379	56.8	1 447	57.7	1 579	59.6
Primary & Secondary	83	3.3	65	2.6	69	2.9	67	2.8	76	3.1	94	3.9	81	3.2	137	5.2
Daycare																
Primary	106	57.3	87	52.7	71	48.6	68	45.9	68	42.5	58	42.3	47	40.9	38	31.4
Secondary	77	41.6	78	42.2	75	51.4	80	54.1	92	57.5	78	56.9	68	59.1	83	68.6
Primary & Secondary	2	1.1	0	0.0	0	0.0	0	0.0	0	0.0	1	0.7	0	0.0	0	0.0

Data source: Minimal Clinical Data (MCD); for patients with multiple hospitalization/admission this is the first hospitalization/admission that is presented.

Table 15 – Proportion of patients with HZ as primary, secondary, primary and secondary diagnosis, by type of stay, 2017-2020

Diagnosis	2017		2018		2019		2020		Total (2008-2020)	
	N	%	N	%	N	%	N	%	N	%
Inpatient										
Primary	879	34.2%	860	34.3%	956	36.4%	706	32.4%	11553	38.9%
Secondary	1 573	61.3%	1 548	61.8%	1 538	58.6%	1 385	63.6%	17035	57.4%
Primary & Secondary	116	4.5%	97	3.9%	130	5.0%	88	4.0%	1103	3.7%
Daycare										
Primary	32	34.4%	31	26.1%	27	27.8%	28	25.9%	661	41.5%
Secondary	60	64.5%	88	73.9%	70	72.2%	80	74.1%	929	58.3%
Primary & Secondary	1	1.1%	0	0.0%	0	0.0%	0	0.0%	4	0.3%

Data source: MCD; for patients with multiple hospitalization/admission this is the first hospitalization/admission that is presented.



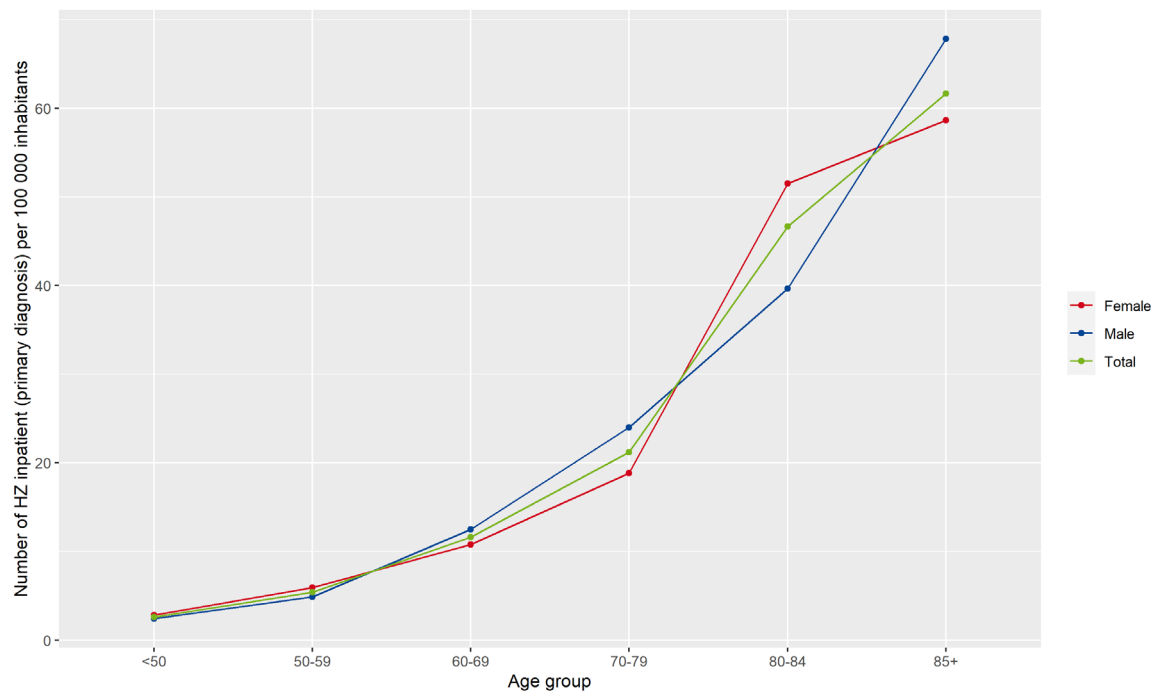
Table 16 – Number of patients hospitalized with HZ as primary, secondary, primary and secondary diagnosis, by sex and age-group, 2019

		Number of inpatients (%)		Number of inpatients per 100 000 inhabitants		Number of inpatients (%)		Number of inpatients per 100 000 inhabitants		Total number of inpatients (%)		Total number of inpatients per 100 000 inhabitants	
		Male		Male		Female		Female					
Primary (n=956)													
<50	86	20.2%	2.44	97	18.3%	2.83	183	19.1%	2.63	17.48			
50–59	39	9.2%	4.88	47	8.9%	5.93	86	9.0%	5.41				
60–69	81	19.1%	12.49	73	13.7%	10.78	154	16.1%	11.62				
70–79	94	22.1%	24.01	88	16.6%	18.85	182	19.0%	21.20				
80–84	52	12.2%	39.65	97	18.3%	51.53	149	15.6%	46.65				
85+	73	17.2%	67.82	129	24.3%	58.65	202	21.1%	61.66				
Total	425	100.0%	7.60	531	100.0%	9.19	956	100.0%	8.41				
Secondary (n=1538)													
<50	55	8.4%	1.56	99	11.2%	2.88	154	10.0%	2.22	31.30			
50–59	55	8.4%	6.89	48	5.4%	6.06	103	6.7%	6.48				
60–69	116	17.7%	17.89	116	13.2%	17.13	232	15.1%	17.50				
70–79	162	24.7%	41.38	169	19.2%	36.21	331	21.5%	38.57				
80–84	94	14.3%	71.67	141	16.0%	74.91	235	15.3%	73.58				
85+	175	26.6%	162.57	308	35.0%	140.02	483	31.4%	147.43				
Total	657	100.0%	11.74	881	100.0%	15.25	1 538	100.0%	13.52				
Primary and secondary (n=130)													
<50	19	30.6%	0.54	13	19.1%	0.38	32	24.6%	0.46	2.22			
50–59	5	8.1%	0.63	4	5.9%	0.51	9	6.9%	0.57				
60–69	4	6.5%	0.62	10	14.7%	1.48	14	10.8%	1.06				
70–79	18	29.0%	4.60	9	13.2%	1.93	27	20.8%	3.15				
80–84	10	16.1%	7.62	13	19.1%	6.91	23	17.7%	7.20				
85+	6	9.7%	5.57	19	27.9%	8.64	25	19.2%	7.63				
Total	62	100.0%	1.11	68	100.0%	1.18	130	100.0%	1.14				

Data source: MCD, for patients with multiple hospitalisation/admission this is the first hospitalisation/admission that is presented.



Figure 3 – Number of patients hospitalized with HZ as primary diagnosis, by sex and age-group, 2019



Data source: MCD

Table 17 – Proportion of inpatients with HZ as principal diagnosis, by year

Number of inpatients	2008		2009		2010		2011		2012		2013		2014		2016		2017		2018		2019		2020		Total	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Principal	1 274	50.8	1 173	46.9	1 077	44.9	1 032	43.4	1 079	44.1	1 057	43.5	1 066	42.5	1 072	40.5	997	38.8	958	38.2	1 092	41.6	789	36.2	12 666	43.0
Not principal	1 232	49.2	1 327	53.1	1 322	55.1	1 347	56.6	1 365	55.9	1 372	56.5	1 442	57.5	1 578	59.5	1 571	61.2	1 547	61.8	1 532	58.4	1 390	63.8	17 025	57.0

Data source: MCD



APPENDIX 2. CLINICAL EFFICACY AND SAFETY

Appendix 2.1. Search strategies for systematic review of efficacy and safety evidence

Appendix 2.1.1. Medline

Date	January 31, 2022
Database	Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions(R) <1946 to January 31, 2022>
Search strategy	
1	(subunit and zoster).ti,kf. 64
2	(adjuvant* and zoster).ti,kf. 100
3	(recombin* and zoster).ti,kf. 173
4	1 or 2 or 3 238
5	(subunit adj3 zoster).ab. 47
6	(adjuvant* adj3 zoster).ab. 76
7	(recombin* adj3 zoster).ab. 149
8	5 or 6 or 7 190
9	"gE/as01b".ab,ti,kf. 5
10	GSK1437173A.ab,ti,kf. 1
11	Shingrix.ab,ti,kf. 76
12	4 or 8 or 9 or 10 or 11 326
13	((herpes or zoster) adj3 vaccin*).ti,kf. 1108
14	exp herpes zoster/ 12547
15	exp vaccines/ 252152
16	14 and 15 1450
17	12 or 13 or 16 2140
18	((systematic review or systematic literature review or systematic scoping review or systematic narrative review or systematic qualitative review or systematic evidence review or systematic quantitative review or systematic meta-review or systematic critical review or systematic mixed studies review or systematic mapping review or systematic cochrane review or "systematic search and review" or systematic integrative review).ti. not comment.pt. not (protocol or protocols).ti. not medline.st.) or (Cochrane Database Syst Rev.ja. and review.pt.) or systematic review.pt. 216699
19	meta-analys*.ti. 144783
20	meta-analysis.pt. 151896



21	exp Technology Assessment, Biomedical/	11748
22	health technology assessment.ti,kf.	2349
23	HtA.ti,kf.	714
24	18 or 19 or 20 or 21 or 22 or 23	324769
25	17 and 24	37
26	randomized controlled trial.pt.	557413
27	controlled clinical trial.pt.	94673
28	randomized.ti,ab.	595215
29	placebo.ti,ab.	231315
30	clinical trials as topic/	199031
31	randomly.ti,ab.	376007
32	trial?.ti.	339007
33	26 or 27 or 28 or 29 or 30 or 31 or 32	1462131
34	exp animal/ not humans/	4951717
35	33 not 34	1346474
36	12 and 35	71
37	limit 36 to yr="2012-Current"	67
38	limit 12 to yr="2012-Current"	278
39	38 not (25 or 37)	204
Comments		

*Appendix 2.1.2. Cochrane*

Date	07/02/2022 04:14:13	
Database	Cochrane	
Search strategy		
#1	(subunit and zoster):ti,kw	47
#2	(adjuvant* and zoster):ti,kw	77
#3	(recombin* and zoster):ti,kw	76
#4	#1 or #2 or #3	142
#5	(subunit NEAR/3 zoster):ab	31
#6	(adjuvant* NEAR/3 zoster):ab	36
#7	(recombin* NEAR/3 zoster):ab	55
#8	#5 or #6 or #7	76
#9	"gE/as01b":ab,ti,kw	0
#10	GSK1437173A:ab,ti,kw	31
#11	Shingrix:ab,ti,kw	15
#12	#4 or #8 or #9 or #10 or #11	177
#13	((herpes or zoster) NEAR/3 vaccin*):ti,kw	330
#14	[mh "herpes zoster"]	477
#15	[mh vaccines]	13711
#16	#14 and #15	115
#17	#12 or #13 or #16	428
#18	#17 with Cochrane Library publication date Between Jan 2012 and Dec 2022	356
Comments		

*Appendix 2.1.3. Embase*

Date	7 Feb 2022
Database	Embase
Search strategy	
#1	subunit:ti,kw AND zoster:ti,kw 96
#2	adjuvant*:ti,kw AND zoster:ti,kw 163
#3	recombin*:ti,kw AND zoster:ti,kw 254
#4	#1 OR #2 OR #3 356
#5	(subunit NEAR/3 zoster):ab 72
#6	(adjuvant* NEAR/3 zoster):ab 123
#7	(recombin* NEAR/3 zoster):ab 234
#8	#5 OR #6 OR #7 290
#9	'ge/as01b':ab,ti,kw 1
#10	gsk1437173a:ab,ti,kw 1
#11	shingrix:ab,ti,kw 114
#12	#4 OR #8 OR #9 OR #10 OR #11 497
#13	((herpes OR zoster) NEAR/3 vaccin*):ti,kw 1573
#14	'varicella zoster vaccine'/exp 3733
#15	'herpes zoster'/exp 29330
#16	'vaccine'/exp 388708
#17	#15 AND #16 4159
#18	#14 OR #17 5464
#19	#12 OR #13 OR #18 6002
#20	#19 AND [2012-2022]/py 3481
#21	#20 NOT ('conference abstract'/it OR 'conference paper'/it OR 'conference review'/it) 2816
#22	#21 NOT [medline]/lim 675
#23	#22 AND ('meta-analysis'/exp OR 'meta-analysis' OR 'systematic review'/exp OR 'systematic review') 36
#24	#22 AND (random*:ab,ti OR placebo*:de,ab,ti OR ((double NEXT/1 blind*):ab,ti)) 47
#25	#22 NOT (#23 OR #24) 598
#26	#20 NOT #21 NOT [medline]/lim 643
Comments	



Appendix 2.2. Excluded studies

Table 18 – Characteristics of excluded studies

Reference	Study design	Number of patients	Age, gender and race	Inclusion criteria	Intervention	Outcome
Kim et al. 2021 ZOE-50/70 ³⁵ NCT01165177 NCT01165229	Pooled data from 2 phase 3 RCT Post hoc analysis, subgroup analysis on Asian population Funded by industry Median FU 4y	≥ 50 yr 2866 TVC ≥ 70 yr 2943 TVC	≥ 50 y 62.0y ± 9.0 Female 60.8% ≥ 70 y 75.95y ± 4.7 Female 51.2%	Inclusion criteria: pooled data from ZOE-50/70 Asian	RZV IM 2 doses (0,2 m) vs placebo	Efficacy and safety
Stadtmauer et al 2021 ³⁶ NCT 01610414 ZOE-HSCT	Phase 3 RCT 1:1 randomized Placebo controlled Triple blinded 28 countries Multicentre (167) Funded by industry Median FU 21m	1846 TVC 1735 2 doses 1721 mTVC	RZV 54.8y ± 11.7 Placebo 55.1 ± 11.4 Female 37.0% White 78.4%	Inclusion criteria: ≥ 18 years Autologous HSCT in previous 50-70 days Exclusion criteria Anti-VZV prophylaxis > 6m history of vaccination varicella or HZ (1y) HIV infection	RZV IM 2 doses (0,1-2m) vs placebo	Immunogenicity by age or underlying disease Efficacy by underlying disease (post-hoc)
Ocran-Appiah et al. 2021 ³⁷ NCT02690207	Phase III b Non randomized Open-label Multinational FU 12m	8687 TVC 97.8% 2e dose	72.6y ± 9.4 Female 60.5% White 73.2%	Inclusion criteria Adults ≥ 50 years prior placebo in ZOE-50 and ZOE-70 No exclusion if HZ episode during pivotal trials Exclusion criteria: confirmed or suspected immunosuppressive or immunodeficient condition	RZV NO CONTROL	Safety (12 m) Secondary: suspected HZ episodes 12 m (clinical confirmation)
Schmader et al. 2019 ³⁸ NCT 02979639	Phase 3 Single arm Open-label 1 country (US) Multicentre (13) FU 12m	6401 TVC 400 returned symptoms sheet	64.6y ± 8.8 Female 58.6% White 82.8%	≥ 50 years	RZV NO CONTROL	Physical functioning SF-36, QOL, Safety Productivity loss Health care resource utilisation
Schmader et al. 2021 ³⁹ NCT 02979639 (same as previous)	Phase 3 Single arm Open label Clinical trial 1 country (US)	401 TVC 97.5% 2e dose	64.6y ± 8.8 Female 58.6% White 82.8%	≥ 50 years	RZV NO CONTROL	Physical functioning SF-36, QOL, Safety Productivity loss Health care resource



Reference	Study design	Number of patients	Age, gender and race	Inclusion criteria	Intervention	Outcome
	Multicentre (13) FU 12m					utilisation
Gruppung et al. 2017⁴⁰ Dagnew et al. 2021⁴¹ NCT02581410	Phase 3 open label Multicenter FU 12m	340	71.1 y $\pm$ 4.9 Female 50.7% White 100%	Inclusion criteria ≥ 65 y Vaccinated with ZVL ≥ 5 years before AND Group matched controls (age, race, sex, medical condition) without ZVL vaccination Exclusion criteria: (to) receive live vaccine (any other drug or vaccine) within 30 d/Immune suppressant or modifying drug longer than 14 days within 180 d/Long acting immune modifying drug within 180 d before/ History of HZ	RZV NO CONTROL ZVL vs Control	Immunogenicity Reactogenicity and safety
Godeaux et al. 2017⁴² NCT01827839	Phase 3, non-randomised, open-label, 2 countries (Canada and Russian federation) Multicenter FU 12m after second dose RZV	96 TVC 93 completed study	64,9y Female 56.6% White 95.8%	Inclusion criteria: Adults ≥ 50 years Prior history of HZ Exclusion criteria: active HZ infection, previous or planned vaccine VZV or HZ confirmed or suspected immunosuppressive or immunodeficiency condition	RZV NO CONTROL	immunogenicity Safety Suspected HZ episodes recorded no assessment of efficacy
Hastie et al. 2021⁴³ NCT 02735915	Phase 3b Open label Single arm 3 countries Multicenter (7) FU 10y	62	82.6 y $\pm$ 4.4 Female 64.5% White 100%	Previous participation in the initial Phase II trial NCT 00434577	(additional) RZV NO CONTROL	Immunogenicity and safety
Maréchal et al. 2018⁴⁴ NCT02045836	Phase 3 Open-label 1:1 randomized controlled 3 countries Multicentre (9) 3/2014-6/2016	864 TVC 1 dose RZV Co-Ad 432 Control 429 2 dose RZV Co-Ad 428	63.2y $\pm$ 8.4 Female 59.6% Caucasian 94.1%	Inclusion criteria: Adults ≥ 50 yr Exclusion criteria prior HZ, VZV or pneumococ vaccine/ history of HZ, pneumococ infection ≤ 5 y/ immunosuppressant or modifying drugs/ cerebrospinal fluid leaks/ cochlear implants/ chronic renal failure/ nephrotic syndrome/ functional or anatomic asplenia	RZV + PPSV23 co-administration (Co-Ad) or RZV after 2 months and second dose after 4 months	Immunogenicity Secondary: safety



Reference	Study design	Number of patients	Age, gender and race	Inclusion criteria	Intervention	Outcome
	FU 12m after second dose RZV	Control 427				
Min et al 2021⁴⁵ NCT03439657	Phase 3 b Open label 1:1 randomized Controlled 4 countries Multicenter FU 12m after last study vaccine dose	912 Co-Ad 119 Control 463	63.15y Female 59.5% White 97.7%	Inclusion criteria: Adults ≥ 50 y Exclusion criteria: prior or planned administration of HZ, VZV or pneumoco vaccine other than study vaccine/ history of HZ, pneumococ infection ≤ 5y/ cerebrospinal fluid leaks/ cochlear implants/ chronic renal failure/ nephrotic syndrome/ functional or anatomic asplenia	RZV + PCV13 co-administration (Co-Ad) or RZV after 2 months and second dose after 4 months	Immunogenicity Secondary: Safety
Schwarz et al. 2017⁴⁶ NCT01954251	Phase 3 Open label 1:1 randomized 3 countries Multicentre (20) FU 12m after last study vaccine dose	829 enrolled 828 TVC Co-Ad 413 Control 415	63.4y±8.6 Female 51.8% White 92%	Inclusion criteria Adults ≥ 50 years Exclusion criteria any non-study vaccine, influenza vaccine, immunosuppressant or immune modifying drugs, VZV or HZ vaccination or history of HZ	RZV + influenza vaccine co-administration (Co-Ad) or RZV after 2 months and second dose after 4 months	Immunogenicity and safety
Strezova et al. 2019⁴⁷ NCT 02052596	Phase 3 Open label 1:1 randomized 1 country (US) Multicentre (13) FU 12m after last study vaccine dose	904 enrolled 903 randomized and first vaccine	Co-Ad 63.4y ± 8.4 Control 63.1y ± 9.0 Female 53.9% White 86.9%	Inclusion criteria: Adults ≥ 50 years Exclusion criteria: History of HZ Any HZ, VZV or Tdap vaccine any time before study or any vaccine against diphtheria or tetanus within 5y preceding Chronic immunosuppressive therapy	RZV + Tdap vaccine co-administration (Co-Ad) or RZV after 2 months and second dose after 4 months	Immunogenicity and safety
Hirzel et al. 2021⁴⁸ NCT 03493776	Single arm Monocenter Prospective FU 2y after last vaccine dose	50 enrolled 49 TVC 45 two doses	65.4 y IQR 59.1-70.6 Female 40.8%	Inclusion criteria ≥ 50 years Single or double lung transplant ≥ 90 days posttransplant Positive varicella zoster IgG antibodies before transplantation	RZV NO CONTROL	Immunogenicity and safety



Reference	Study design	Number of patients	Age, gender and race	Inclusion criteria	Intervention	Outcome
L'Huillier et al. 2021⁴⁹	Prospective interventional monocenter study FU 3m after second dose RZV	51 patients Met inclusion criteria 23 patients consent	38y (31.3-55.8) Female 52.2% White 87%	Inclusion criteria ≥ 18 years SOT and functioning allograft ≥ 90 days posttransplant Exclusion criteria history of HZ or varicella/ positive IgG against VZV (x2)/ prior varicella or HZ vaccine/ CMV viremia/ other immunodeficiency/ treatment for rejection or Ig treatment past 30 days or anticipated	RZV NO CONTROL	Safety
Baumrin et al. 2021⁵⁰	Prospective Observational cohort Single center FU ≥30d post vaccination	178 enrolled 158 dose 1 150 dose 2	55.0y (±13.83) Female 58%	Inclusion criteria: ≥ 18 years Allogeneic HCT 9-24 months post Exclusion criteria: Disease relapse	RZV NO CONTROL Cohort A 9-12m post HSCT Cohort B 13-24m post HSCT	Primary: reactogenicity and safety in TVC Secondary: incidence and severity of GVHD Incidence rates of HZ in mTVC
Satyam et al. 2020⁵¹	Prospective observational Monocentre (USA) Median FU 207d	67 IBD patients ≥ 1dose RZV 82% 2 doses	63y (IQR 56-68.5) Female 54%	Adults with Chron's disease or colitis ulcerosa	RZV NO CONTROL	Outcome: IBD flare (1 patient) Secondary: rates of local and systemic adverse reactions after vaccination
Stevens et al. 2020⁵²	Retrospective Cohort Monocentre Mean FU 13.2w after vaccination	403 55.1% 2 doses	67.2y± 10.6 Female 75% White 85.6%	Patients with rheumatoid arthritis or systemic rheumatic disease	RZV NO CONTROL	Incidence of disease flare
Lenfant et al. 2021⁵³	Retrospective cohort Monocentre 2/2018-3/2020 Median FU 30w	622 146 (1 dose) 476 (2 doses)	67y Female 67%	Inclusion criteria ≥ 18 years At least one doses RZV In FU at rheumatology dept	RZV NO CONTROL	Safety
Gupta et al. 2022⁵⁴	Retrospective Cohort Monocenter	65 (≥1 dose)	68y (44-89) Female 86.2% White 78.5%	Inclusion criteria ≥18 years Rheumatic disease Exclusion criteria:	RZV NO CONTROL	Safety (self reported adverse events and 'flares')



Reference	Study design	Number of patients	Age, gender and race	Inclusion criteria	Intervention	Outcome
	FU 3m ater each RZV dose			Osteoarthritis and fibromyalgia		
Barghash et al. 2021⁵⁵	Retrospective Cohort Single centre Median FU 36w	65 (≥1 dose) 46 (2 doses)	66y ± 12.7 Female 35% White 75%	Inclusion criteria Heart transplant recipients (Vaccinated between 9/2018 and 7/2019)	RZV NO CONTROL	Safety (AE)
Hesse et al. 2019⁵⁶	Postlicense passive surveillance system VAERS (Vaccine adverse Event Reporting system) FU 8m	4381 reports	50-59y 21.8% 60-69y 33.5% 70-79y 22.6% Female 65.5%		RZV NO CONTROL	Safety
Pirrotta et al; 2021⁵⁷	Post marketing surveillance GSK safety database FU 2.5y	3274 reports	50-69y 36.4 % >70y 28.2 % Female 59%		RZV NO CONTROL	Safety
Tavares-Da-Silva et al. 2020⁵⁸	Post marketing surveillance 13/10/2017-10/2/2019 GSK safety database and SMM tool VAERS, Canada vigilance adverse reaction and EMA Eudravigilance FU 16m	15638 reports 37 697 AE	50-69y 62.1% Female 66.7%		RZV NO CONTROL	Safety
Lal et al. 2018⁵⁹ NCT 01751165	Phase 3 Open label 1:1:1 randomized 2 countries Multicentre FU 12m post dose 2	354 adults	64.2y ± 8.9 Female 69% White 99%	Inclusion criteria ≥ 50y Exclusion criteria other live or non-replicating vaccine/ history of HZ, vaccine VZV or HZ/ Immunosuppressive or Imune mediating drugs or disease	RZV only 2-6-12m apart	Safety

AE: adverse events, Co-ad: co-administration, d: days, EMA: European Medicines Agency; FU: follow-up, m: months, mTVC: modified vaccinated cohort, PCV13: pneumococcal conjugate vaccine, PPSV23: pneumococcal polysaccharide vaccine, RZV: recombinant zoster vaccine, SMM: signal mining and management, Tdap: Tetanus-Diphtheria-Pertussis vaccine, TVC: total vaccinated cohort, VAERS: vaccine adverse event reporting system, w:weeks, y:years.



Appendix 2.3. Quality appraisal of included studies

Table 19 – Quality appraisal of included RCTs

Bias	Level	Support for judgement
ZOE-50⁶⁰, ZOE-70⁶¹		
Random sequence generation (selection bias)	• Low risk of bias	• Online centralized randomization system
Allocation concealment (selection bias)	• Low risk of bias	• Online centralized randomization system • Demographic characteristics similar in both groups at baseline
Blinding of participants and personnel (performance bias)	• Low risk of bias	• The appearance of the reconstituted RZV vaccine differed from the placebo solution but injections were done by study staff who did not participate in any study assessment. The investigators, participants, and assessors were unaware of whether vaccine or placebo had been administered
Blinding of outcome assessment (detection bias)	• Low risk of bias	• Assessors were unaware of whether vaccine or placebo had been administered. • Standardized definition of main outcomes, suspected cases of HZ confirmed by PCR or ascertainment committee
Incomplete outcome data (attrition bias)	• Low risk of bias (for outcome reactogenicity unclear risk of bias, but probably low)	• The primary analysis was not by intention to treat: <ol style="list-style-type: none"> 1. A small number (749/16,160 in ZOE50; 913/14,816 in ZOE70) were excluded for deviations from Good Clinical Practice standards at 2 and 1 study centres, respectively. 2. The primary analysis was carried out in the modified vaccination cohort (i.e. exclusion of participants who did not receive the second dose of vaccine or who had HZ within 1 month after the second dose). The modified cohort represented 95.8% and 94.7% of the total vaccinated cohort in ZOE50 and ZOE70, respectively. <ul style="list-style-type: none"> • But the analysis based on total cohort yielded same results as in the modified cohort • Reactogenicity was evaluated in sub-cohort: 926 participants (58%) of ZOE-50 (all participants who were 70 years of age or older and randomly selected participants in two other age groups (50 to 59 years and 60 to 69 years) and 1025 participants (7.4%) of ZOE-70 (a randomly selected subgroup of age-stratified participants)
Selective reporting (reporting bias)	• Low risk of bias	• Primary, secondary and exploratory objectives defined in the study protocol
Overall	• Low risk of bias	
Publications with analysis on pooled ZOE-50 and ZOE-70 data^{41, 62-68}		



Random sequence generation	• Same as ZOE-50 and ZOE-70	• Same as ZOE-50 and ZOE-70
Allocation concealment		
Blinding of participants and personnel	• Low risk of bias	
Blinding of outcome assessment		
Incomplete outcome data		
Selective reporting (reporting bias)	• Unclear risk of bias	• For publications with post-hoc analysis on pooled ZOE-50/70 data ^{41, 62, 67, 68}
Other	• Unclear risk of bias	• In the quality of life assessments for the ZOE-50 population ⁶⁴ the authors mention 9 cases on 7340 individuals 'at the end of study analysis', however the original ZOE-50 paper mention only 6 cases on 7344 individuals in the modified vaccinated cohort. This might be different due to a difference in follow-up time, however it is not specified in the publication.
ZOE-HSCT (Zoster – 002)⁶⁹		
Random sequence generation (selection bias)	• Low risk of bias	• Centralized randomization system
Allocation concealment (selection bias)	• Low risk of bias	<ul style="list-style-type: none"> • Centralized randomization system • A minimization procedure was applied to achieve a balanced representation of study groups across 6 different factors: age, underlying diagnosis, post- transplantation antineoplastic maintenance therapy, anticipated duration of post-transplantation antiviral prophylaxis, center and sex • The study groups had similar baseline demographic characteristics
Blinding of participants and personnel (performance bias)	• Low risk of bias	<ul style="list-style-type: none"> • Vaccine prepared and administered by study staff who did not participate in any study end-point assessment • The investigators, participants, and assessors were unaware of whether vaccine or placebo had been administered
Blinding of outcome assessment (detection bias)	• Low risk of bias	<ul style="list-style-type: none"> • Assessors were unaware of whether vaccine or placebo had been administered. • Standardized definition of main outcomes, suspected cases of HZ confirmed by PCR or ascertainment committee
Incomplete outcome data (attrition bias)	• Unclear risk of bias, but probably low	<ul style="list-style-type: none"> • The primary analysis was not by intention to treat: <ul style="list-style-type: none"> - A small number were excluded because they did not meet eligibility criteria (22/1868) - The primary analysis was carried out in the modified vaccination cohort The modified cohort represented 93% of total vaccinated cohort. But the analysis based on total cohort yielded similar results as in the modified cohort
Selective reporting (reporting bias)	• Low risk of bias	• Primary, secondary and exploratory objectives defined in the study protocol



Overall	• Low risk of bias	
Zoster-028 (solid tumours)⁷⁰		
Random sequence generation (selection bias)	• Low risk of bias	• Web based central randomization system
Allocation concealment (selection bias)	• Low risk of bias	• Randomization algorithm used a minimization procedure accounting for age, study visit, country, and sex • Demographic characteristics were comparable between study arms.
Blinding of participants and personnel (performance bias)	• Low risk of bias	• Vaccine prepared and administered by study staff who did not participate in any study end-point assessment • The vaccine recipient and those responsible for the evaluation of any study endpoint (e.g., safety and reactogenicity) were all unaware of which vaccine was administered • No blinded in regards time of vaccination relative to chemotherapy (PreChemo vs OnChemo).
Blinding of outcome assessment (detection bias)	• Low risk of bias	• Those responsible for the evaluation of any study endpoint (e.g., safety and reactogenicity) were all unaware of which vaccine was administered • Standardized definition of main outcomes
Incomplete outcome data (attrition bias)	• Unclear risk of bias, but probably low	• The primary analysis (safety) was carried out in the total vaccinated cohort, which consisted of 89% of the enrolled and randomized participants. • Some participants who were randomized to the Pre-Chemo-stratum and were required to wait 8-30 days after vaccination before they could start chemotherapy chose to withdraw so as to proceed to chemotherapy immediately, however the percentage of withdrawal was similar in RZV and placebo group
Selective reporting (reporting bias)	• Low risk of bias	• Primary, secondary and exploratory objectives defined in the study protocol
Overall	• Low risk of bias	
Zoster-039 (haematological malignancies)⁷¹		
Random sequence generation (selection bias)	• Low risk of bias	• Online, centralized randomization system
Allocation concealment (selection bias)	• Low risk of bias	• Online, centralized randomization system • Demographic characteristics are balanced between groups
Blinding of participants and personnel (performance bias)	• Low risk of bias	• Vaccine or placebo administrations were done by unmasked authorized medical personnel who did not participate in clinical evaluation • The investigators, participants, and assessors were unaware of whether vaccine or placebo had been administered
Blinding of outcome assessment (detection bias)	• Low risk of bias	• Assessors were unaware of whether vaccine or placebo had been administered.



		<ul style="list-style-type: none"> Standardized definition of main outcomes, suspected cases of HZ confirmed by PCR or ascertainment committee
Incomplete outcome data (attrition bias)	<ul style="list-style-type: none"> Low risk of bias 	<ul style="list-style-type: none"> The primary analysis (safety) was carried out in the total vaccinated cohort, which consisted of 99% of the enrolled and randomized participants
Selective reporting (reporting bias)	<ul style="list-style-type: none"> Low risk of bias 	<ul style="list-style-type: none"> Primary, secondary and exploratory objectives defined in the study protocol
Overall	<ul style="list-style-type: none"> Low risk of bias 	
Zoster-041 (renal transplant)⁷²		
Random sequence generation (selection bias)	<ul style="list-style-type: none"> Unclear risk of bias, but probably low 	<ul style="list-style-type: none"> Randomization algorithm
Allocation concealment (selection bias)	<ul style="list-style-type: none"> Unclear risk of bias, but probably low 	<ul style="list-style-type: none"> Randomization algorithm The randomization algorithm included the following minimization factors: age (18-29, 30-49, or ≥50 YOA), gender, participant's highest panel reactive antibody (PRA) or calculated PRA (cPRA) score at/prior to transplant, and maintenance immunosuppressive therapy (use of mycophenolate compounds [MC], calcineurin inhibitors or sirolimus [CIS], or corticosteroids [CS]) Demographic characteristics were balanced between study groups
Blinding of participants and personnel (performance bias)	<ul style="list-style-type: none"> Unclear risk of bias, but probably low 	<ul style="list-style-type: none"> The vaccine recipient and those responsible for the evaluation of any study endpoint (e.g., safety and reactogenicity) were all unaware of which vaccine was administered
Blinding of outcome assessment (detection bias)	<ul style="list-style-type: none"> Unclear risk of bias, but probably low 	<ul style="list-style-type: none"> The vaccine recipient and those responsible for the evaluation of any study endpoint (e.g., safety and reactogenicity) were all unaware of which vaccine was administered
Incomplete outcome data (attrition bias)	<ul style="list-style-type: none"> Low risk of bias 	<ul style="list-style-type: none"> The primary analysis (safety) was carried out in the total vaccinated cohort, which consisted of > 99% of the enrolled and randomized participants:
Selective reporting (reporting bias)	<ul style="list-style-type: none"> unclear risk of bias, but probably low 	<ul style="list-style-type: none"> No full protocol available online
Overall	<ul style="list-style-type: none"> Low risk of bias 	


Table 20 – Risk of Bias evaluation for included observational studies

Bias	Level	Support for judgement
ZOE-LTFU⁷³		
Bias due to confounding	Unclear risk of bias	Extension study of ZOE-50 and ZOE-70, follow-up of selected vaccinated patients compared with matched historical unvaccinated controls, initial randomization of ZOE-50/70 broken Historical controls from the placebo group in the ZOE-50/70 studies, adjusted for age and region at randomization during the ZOE-50/70 studies
Bias in selection of participants into the study	Unclear risk of bias	Only 7413 (50.6%) of ZOE-50/70 participants enrolled in ZOE-LTFU, there were numerous exclusion criteria and no data on demographic characteristics in the selected vaccinated patients is provided, i.e. unclear if they are similar to the characteristics in ZOE-50/70
Bias in classification of interventions	Low risk of bias	All patients in follow-up are vaccinated (participants of ZOE-50/70), open label
Bias due to deviations from intended interventions	Low risk of bias	All patients in follow-up are vaccinated (participants of ZOE-50/70)
Bias due to missing data	Low risk of bias	In year 7 after vaccination 2.4% of patients lacking data in the RZV group
Bias in measurement of outcomes	Low risk of bias	Standardized definition of main outcomes, suspected cases of HZ confirmed by PCR or ascertainment committee
Bias in selection of the reported result	Unclear risk of bias	Primary, secondary and exploratory objectives defined in the study protocol, but not all outcomes are assessed in this intermediate report e.g. no data on PHN reported
Sun, Kim 2021⁷⁴		
Bias due to confounding	Low risk	Data adjusted using Inverse Probability Weighting (IPW) for age, sex, race/ethnicity, region, prior ZVL, antiviral use, healthcare utilisation and Charlson comorbidity index
Bias in selection of participants into the study	Low risk	Health care database of over 200 million individuals enrolled in commercial insurance, Medicare advantage, or Medicare part D. Comparisons between US census and OptumLabs Data Warehouse (OLDW) demonstrate distribution in age, sex, race/ethnicity and region are comparable between the two. OLDW is nationally representative for commercial enrollees. Vaccinated individuals were older, more often Medicare enrollees, had more healthcare utilisation and were slightly more often female, more often white Data adjusted using IPW for age, sex, race/ethnicity, region, prior ZVL, antiviral use, healthcare utilisation and Charlson comorbidity index
Bias in classification of interventions	Low risk	Receipt of RZV was identified by a current procedural terminology (CPT) code or in pharmacy claims by the brand name for RZV



Bias	Level	Support for judgement
Bias due to deviations from intended interventions	Low risk	A patient was deemed vaccinated after receipt of the second dose of RZV. A second dose was valid if it occurred 30-120 days after the first dose. History of systemic antiviral use was adjusted for.
Bias due to missing data	Low risk	Missing data unlikely
Bias in measurement of outcomes	Low risk	Diagnosis HZ by ICD 9 th or 10 th revision code – in any clinical setting or using any diagnostic position from physician claims and facility claims.
Bias in selection of the reported result	Low risk	The reported effect estimate is not likely to be selected from multiple outcome measurements, multiple analysis of the intervention outcome relationship nor from different subgroups
Overall	Low risk	At least one domain moderate risk
Sun, Jackson 2021⁷⁵		
Bias due to confounding	Low risk	Inverse probability weighting (IPW) was used to control for confounding Time-fixed covariates (sex, race, ethnicity, and prior ZVL), time-varying covariates (age, healthcare utilisation, Deyo Comorbidity Index and systemic antiviral use)
Bias in selection of participants into the study	Low risk	Kaiser Permanente Hawaii: 1 hospital and 27 medical offices serving 18% of population of Hawaii Vaccinated individuals are older, more often Asian (and less native Hawaiian or other Pacific Islander), had more inpatient care Imbalance overcome by inverse probability weighting
Bias in classification of interventions	Low risk	Receipt of RZV was identified by searching for the brand name for RZV within an individual's vaccination record from their electronic health records
Bias due to deviations from intended interventions	Low risk	The exposure of interest was receipt of 2 valid doses of RZV. A second dose was valid if it occurred 30-120 days after the first dose. History of systemic antiviral use was adjusted for.
Bias due to missing data	Low risk	Missing data unlikely
Bias in measurement of outcomes	Low risk	Outcome: first diagnosis of HZ that occurred during the study follow-up; medical record ICD 10 th revision code HZ (ICD-10 B2.xx)
Bias in selection of the reported result	Low risk	The reported effect estimate is not likely to be selected from multiple outcome measurements, multiple analysis of the intervention outcome relationship nor from different subgroups
Overall	Low risk	
Izurieta 2021⁷⁶		
Bias due to confounding	Low risk	Inverse probability weighting to balance all covariates across the 3 cohorts



Bias	Level	Support for judgement
		<p>Confounders: age, sex, race, socio-economic status, functional immunocompromising chronic conditions (immunocompromising drugs as a time-varying covariate), frailty characteristics, health utilization and preventive service utilization (extensive list)</p> <ul style="list-style-type: none">• Age (65-79; 80+)• Sex (Male; Female)• Race (White; Black; Other)• Census Region (West; Midwest; South; Northeast; Other)• Reason for entrance into Medicare (Aged without ESRD/other; Disabled without ESRD)• Low income subsidy status (Has LIS; Does not have LIS)• Area Deprivation Index (ADI): We will use ADI quintile groups (0-19; 20-39; 40-59; 60-79; 80+; Missing)• Hospitalisation stay in 1 year prior• Outpatient-ER visit in 1 year prior• General medical visit (Used to identify office and consultation visits using E/M codes that pertains to only medical office visits and consultations without overlapping IP + OP-ER claims. This will be used to represent the combination of OP-Non-ER visits and Physician Office visits covariates.)• ZVL vaccine in the 5 years prior to index date• Vaccines (defined as separate binary variables):<ul style="list-style-type: none">○ Pneumococcal vaccine○ Hepatitis B vaccine○ Tetanus vaccine• Health Conditions (defined as separate binary variables):<ul style="list-style-type: none">○ Asthma○ Blood disorders○ Chronic lung disease○ Diabetes○ Heart disease○ Kidney disorders○ Liver disorders○ Neurological conditions○ Other malignant neoplasms



Bias	Level	Support for judgement
		<ul style="list-style-type: none">○ Anaphylaxis• Frailty Conditions (defined as separate binary variables):<ul style="list-style-type: none">○ Dementia○ Falls○ Fractures○ Home oxygen○ Urinary catheter○ Walker use○ Wheelchair use• Other Risk Covariates (defined as separate binary variables):<ul style="list-style-type: none">○ Alcohol risk○ Medical nutrition therapy○ Obesity prevention/control○ Tobacco risk• Preventative Services:<ul style="list-style-type: none">○ General preventative services (defined as separate binary variables):<ul style="list-style-type: none">▪ Annual wellness visit (AWV)▪ Counseling & Health risk assessment○ Specific preventative services (defined as ordinal variable; 0, 1, 2, and 3+)<ul style="list-style-type: none">▪ Aortic aneurism risk▪ Blood pressure▪ Bone mass measurements▪ Cardiovascular disease screening▪ Colorectal cancer screening▪ Counseling to prevent STIs▪ Depression risk▪ Dermatological treatment▪ Diabetes screening▪ Diabetes self-management training (DSMT)▪ Diabetic foot care▪ Glaucoma Screening▪ Gynecological exam▪ Hepatitis C virus (HCV) screening



Bias	Level	Support for judgement
		<ul style="list-style-type: none"> Intensive behavioral therapy (IBT) for cardiovascular disease Lung cancer prevention Prostate cancer screening Screening mammography Vision, hearing, dental screening <p>BUT Reported vaccine effectiveness is not adjusted for covariates, is this a problem since covariates are balanced over the cohorts?</p>
Bias in selection of participants into the study	Low risk	<p>Medicare population =15 million beneficiaries (eligible for RZV vaccination) , Vaccinated individuals were more likely to have no low-income subsidy status, lower area deprivation index of residence, less likely no general medical visits, more likely annual wellness visit, more likely more preventive services Inverse probability weighting to balance all covariates across the 3 cohorts</p>
Bias in classification of interventions	Low risk	NDC (national drug codes) in Medicare part D claims, prospective data collection
Bias due to deviations from intended interventions	Low risk	Adjustment for co-interventions (extensive list)
Bias due to missing data	Low risk	Missing data is unlikely
Bias in measurement of outcomes	Low risk	Community HZ defined by a claim in the institutional outpatient or professional PB setting with an ICD-10 diagnosis code for HZ (B020, B021, B022.x, B027-B029) in any position with a claim for HZ specific antiviral identified using NDCs within 7 days of diagnosis (sensitivity analysis same clinical definition without requiring prescription for antivirals), secondary outcome OZ and PHN
Bias in selection of the reported result	Low risk	The reported effect estimate is not likely to be selected from multiple outcome measurements, multiple analysis of the intervention outcome relationship nor from different subgroups
Overall	Low risk	
Lu 2021⁷⁷		
Bias due to confounding	Low risk	<p>Inverse probability weighting to adjust for measured confounding Confounders were designated as time-fixed (sex, race, region, insurance type and prior ZVL), and time-varying (age, healthcare utilisation, age-adjusted Charlson Comorbidity Index and systemic antiviral use</p>
Bias in selection of participants into the study	Low risk	Almost 5 000 000 individuals included, OLDW (commercial insurance, Medicare part D or Medicare advantage



Bias	Level	Support for judgement
		Vaccinated individuals were older, slightly more often female, more frequently white, more frequently Medicare enrollees, and had more health utilisation
Bias in classification of interventions	Low risk	Receipt of RZV was identified by a current procedural terminology (CPT) code or in pharmacy claims by the brand name for RZV
Bias due to deviations from intended interventions	Low risk	The exposure of interest was receipt of 2 valid doses of RZV. A second dose was valid if it occurred 30-120 days after the first dose. History of systemic antiviral use was adjusted for.
Bias due to missing data	Low risk	Missing data unlikely
Bias in measurement of outcomes	Low risk	Outcome first code for HZO (ICD-9 053.2x, ICD-10 B02.3x)
Bias in selection of the reported result	Low risk	The reported effect estimate is not likely to be selected from multiple outcome measurements, multiple analysis of the intervention outcome relationship nor from different subgroups
Overall	Low risk	
Khan 2021⁷⁸		
Bias due to confounding	Low risk	<p>Non-time-varying covariates: age, gender; race, Inflammatory Bowel Disease (IBD) diagnosis and geographic locations, Charlson Comorbidity Index, and VA health care utilization</p> <p>Time-varying covariates for each 60-day interval: use of 7 IBD medications, Intensity of prednisone use, oral prednisone use within 30 days, proxy for IBD flare-up, the prior HZ vaccination status was defined as a dummy variable</p> <p>Cox regression models, adjusting for all non-time-varying and time-varying covariates mentioned above</p>
Bias in selection of participants into the study	Low risk	<p>Participants: 7008 eligible patients with IBD in the 50- to 60-year group and 26,292 in >60-year groups,</p> <p>Comparing vaccinated and unvaccinated individuals in the 50- to 60-year group those who received a full dose or single dose were older, were more likely to be white, had more comorbidities, were more likely to be in the Midwest and North Atlantic, and were more likely to have > 13 visits in the past year. Similar differences were observed among those >60 years old, except that those who received a full dose or single dose were younger and the numerically similar difference in IBD type distribution reached statistical significance in that age group</p> <p>Cox regression model without any interaction, after adjusting for other baseline and time-varying covariates</p>



Bias	Level	Support for judgement
Bias in classification of interventions	Low risk	Receipt of RZV obtained from inpatient and outpatient ICD-9-CM and ICD-10-CM (pharmacy, procedures, ...)
Bias due to deviations from intended interventions	Low risk	Adjusting for time-varying covariates like prednisone and other IBD medication use.
Bias due to missing data	Low risk	Missing data unlikely
Bias in measurement of outcomes	Low risk	ICD-9-CM and ICD-10-CM (diagnosis codes, encounters, procedures, pharmacy)
Bias in selection of the reported result	Low risk	The reported effect estimate is not likely to be selected from multiple outcome measurements, multiple analysis of the intervention outcome relationship nor from different subgroups
Overall	Low risk	
Kochhar 2021⁷⁹		
Bias due to confounding	Moderate risk	Explorys, a multi-institution de-identified electronic health record database, allows searches within selected cohorts (demographics, medications, vital signs and procedures). Specific searches included evaluation of age groups, gender, race and co-morbid conditions (diabetes and cardiovascular disease). Descriptive characterization of baseline demographics was performed and Chi-square test to independence was used to analyze the risk of HZ among the groups. No method to prevent or overcome confounding
Bias in selection of participants into the study	Moderate risk	Baseline demographics in different groups are not always similar. In the IBD cohort patients that were more likely to receive 2 doses vaccines included patients aged > 65 years, and patients with obesity, hypertension, hyperlipidemia and coronary artery disease. In control cohort patients (no IBD, vaccinated or unvaccinated) that were more likely to receive 2 doses of RZV included Caucasian race, private insurance and patients with hypertension, hyperlipidemia, obesity and coronary artery disease
Bias in classification of interventions	Low risk	"Specific diagnoses, procedures and medications are mapped into the systematized nomenclature of medicine clinical terms (SNOMED-CT). Each unique search allow users to further specify associated medications, comorbidities, demographics and vital signs"
Bias due to deviations from intended interventions	Low risk	Specific diagnoses, procedures and medications are mapped into the systematized nomenclature of medicine clinical terms (SNOMED-CT). Each unique search allow users to further specify associated medications, comorbidities, demographics and vital signs



Bias	Level	Support for judgement
Bias due to missing data	Low risk	Only hospital based prescriptions in Explorys, small chance missing data from immunisation outside hospital network system, but order can be identified even if administration outside hospital
Bias in measurement of outcomes	Low risk	Prospectively maintained dataset Specific diagnoses, procedures and medications are mapped into the systematized nomenclature of medicine clinical terms (SNOMED-CT). Each unique search allow users to further specify associated medications, comorbidities, demographics and vital signs"
Bias in selection of the reported result	Low risk	The reported effect estimate is not likely to be selected from multiple outcome measurements, multiple analysis of the intervention outcome relationship nor from different subgroups
Overall	Moderate risk	
Goud 2021⁸⁰		
Bias due to confounding	Moderate risk	Cohort: To reduce potential confounding from specific frail Medicare populations that could have a different association between vaccination and GBS, beneficiaries could not be undergoing long-term dialysis therapy, or admitted to a nursing home, skilled nursing facility, or in hospice at any point during the study period. In addition we excluded beneficiaries with a historical GBS diagnosis in any diagnosis position from any provider within 6m prior to first RZV vaccination and beneficiaries receiving RZV administration inconsistent with recommended dosing in the package insert. Self-controlled case study: self-controlled
	Low risk	
Bias in selection of participants into the study	Low risk	Cohort: Demographic characteristics comparable, except for age: ZVL vaccinated: more younger patients: 65-69 yearsself-controlled case study: self-controlled
Bias in classification of interventions	Low risk	"RZV and ZVL vaccinations were identified using national drug codes from Medicare part D claims. To ensure complete capture of RZV vaccinations, we required continuous Medicare Fee-for-Service, and part D enrolment through 6 months after the last RZV vaccination, end of study period or death, whichever occurred earlier." Retrospective design
Bias due to deviations from intended interventions	Low risk	"RZV and ZVL vaccinations were identified using national drug codes from Medicare part D claims. To ensure complete capture of RZV vaccinations, we required continuous Medicare Fee-for-Service, and part D enrolment through 6 months after the last RZV vaccination, end of study period or death, whichever occurred earlier"
Bias due to missing data	Moderate risk	Possibly missing data from unvaccinated control group and less follow-up



Bias	Level	Support for judgement
Bias in measurement of outcomes	Low risk	Data from Medicare enrolment and claims database, enrolment database (EDB) and common working file (CWF) to identify participants, and then had an incident case of GBS
Bias in selection of the reported result	Low risk	The reported effect estimate is not likely to be selected from multiple outcome measurements, multiple analysis of the intervention outcome relationship nor from different subgroups
Overall	Moderate risk	



Appendix 2.4. Vaccine efficacy and safety

Table 21 – Vaccine efficacy against HZ in immunocompetent individuals ≥50 years (modified total vaccinated cohort) in different subgroups

Study	Patients	FU	Incidence rate of HZ per 1000 person-years		Efficacy %	95%CI
			RZV (n/PY)	C (n/PY)		
ZOE-Frailty study⁶³	Non-frail	±4y	0.4 (8/21 803)	8.8 (188/21 443)	95.8	91.6-98.2
	Pre-frail		0.8 (18/21 842)	8.6 (191/22 250)	90.4	84.4-94.4
	Frail		1.0 (5/5158)	9.9 (46/4663)	90.2	75.4-97.0
	Unknown		0.0 (0/186)	25.8 (5/194)	100.0	14.6-100.0
ZOE-50/70 ≥1 selected medical condition at enrolment⁶⁷	Hypertension	Not specified	0.8 (21/27 203)	9.5 (254/26 752)	91.9	87.3-95.1
	Osteoarthritis and/or vertebral disorder		0.9 (16/18 733)	9.6 (178/18 604)	91.1	85.1-95.0
	Dyslipidemia		0.9 (15/17 578)	9.7 (169/17 507)	91.2	85.1-95.2
	Diabetes		0.8 (7/8724)	9.2 (80/8653)	91.2	81.1-96.6
	Osteoporosis/osteopenia		0.9 (5/5552)	13.0 (72/5552)	92.9	82.7-97.8
	Gastroesophageal reflux disease		1.2 (6/5010)	9.1 (44/4816)	86.9	69.0-95.4
	Sleep disorder		0.8 (4/4899)	11.7 (56/4803)	93.1	81.4-98.2
	Prostatic diseases		0.4 (2/4648)	10.7 (50/4667)	96.1	85.1-99.5
	Hypothyroidism		0.9 (4/4387)	6.6 (28/4241)	86.2	60.4-96.5
	Depression		0.5 (2/3767)	8.1 (29/3568)	93.4	74.1-99.2
	Coronary heart disease		0.3 (1/3774)	8.9 (35/3913)	97.0	82.3-99.9
	Cataract		1.3 (4/2965)	14.0 (41/2931)	90.4	73.4-97.5
	Asthma		1.2 (3/2421)	10.9 (28/2576)	88.8	63.6-97.8
	Respiratory disorders		1.4 (3/2221)	8.7 (17/1944)	84.5	46.4-97.1
	Renal disorders		0.9 (1/1065)	7.0 (7/1002)	86.6	-4.5-99.7
	1 medical condition		0.4 (5/12 269)	8.9 (109/12 213)	95.4	89.0-98.5
	2 medical conditions		0.6 (7/11 797)	8.3 (97/11 746)	92.8	84.7-97.2
	3 medical conditions		0.9 (8/8804)	9.6 (88/9163)	90.5	80.5-96.0
	At least 3 medical conditions		1.0 (19/19 417)	10.3 (199/19 338)	90.5	84.8-94.4
	At least 4 medical conditions		1.0 (11/10 613)	10.9 (111/10 176)	90.6	82.4-95.4
	At least 5 medical conditions		1.0 (5/5133)	11.0 (52/4742)	91.2	78.0-97.3
	At least 6 medical conditions		1.0 (2/2039)	10.5 (20/1910)	90.9	62.5-99.0
ZOE-50/70 , ≥1 pIMD⁴¹	≥1 pre-existing potential immune mediated disease at enrolment	4.4y	1.1 (4/3612)	11.1 (38/3409)	90.5	73.5-97.5
ZOE- LTFU, Zoster-049⁷³	Extension ZOE-50/70, open label, ≥ 50y	7.1y	0.8 (59/72 745)	8.9 (651/72 745)	90.9	88.2-93.2

CI: confidence interval, FU: follow-up, HZ: Herpes Zoster, RZV: recombinant zoster vaccine, LTFU: long-term follow-up, n: number of HZ cases, pIMD: potential immune-mediated disease, PY: person-years.


Table 22 – Reactogenicity in immunocompromised patients

Study	RZV n/N	% (95%CI)	Placebo n/N	% (95%CI)	RZV n/N	% (95%CI)	Placebo n/N	% (95%CI)
Any local reaction				Local reactions grade 3				
Zoster-002 ZOE-HSCT⁶⁹	773/901	85.8 (83.3-88)	93/892	10.4 (8.5-12.6)	128/901	14.2 (12.0-16.7)	3/892	0.3 (0.1-1.0)
Zoster-028 Solid Tumour⁷⁰	94/112	83.9 (75.8-90.2)	7/110	6.4 (2.6-12.7)	13/112	11.6 (6.3-19.0)	0/110	0 (0.0-3.3)
Zoster-039 Haematological Malignancies⁷¹	233/278	83.8 (78.9-87.9)	48/274	17.5 (13.2-22.5)	32/278	13.3 (9.5-17.9)	0/274	0.0 (0.0-1.3)
Zoster-041 Renal Transplant⁷²	115/132	87.8 (80.9-92.9)	12/132	9.1 (4.8-15.3)	14/132	10.7 (6.0-17.3)	0/132	0 (0.0-2.8)
Any systemic reaction				Systemic reactions grade 3				
Zoster-002 ZOE-HSCT⁶⁹	678/901	75.2 (72.3-78.0)	455/892	50.9 (47.6-54.2)	119/901	13.2 (11.1-15.6)	54/892	6.0 (4.6-7.8)
Zoster-028 Solid Tumour⁷⁰	91/112	81.3 (72.8-88.0)	73/110	66.4 (56.7-75.1)	25/112	22.3 (15.0-31.2)	17/110	15.5 (9.3-23.6)
Zoster-039 Haematological Malignancies⁷¹	206/278	74.1 (68.5-79.1)	134/274	48.9 (42.8-55.0)	43/278	15.5 (11.4-20.3)	17/274	6.2 (3.7-9.7)
Zoster-041 Renal Transplant⁷²	90/132	68.7 (60.0-76.5)	73/132	55.3 (46.4-66.0)	13/132	9.9 (5.4-16.4)	11/132	8.3 (4.2-14.4)

CI: confidence interval, HSCT: Haematological Stem Cell Transplantation, n: number of events, N: number of participants, RZV = recombinant zoster vaccine



Table 23 – Risk of Serious Adverse Events, Meta-analysis

Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With placebo	With RZV		Risk with placebo	Risk difference with RZV
serious adverse event											
32215 (6 RCTs)	not serious	not serious	not serious	not serious	none	⊕⊕⊕⊕ High	2301/16113 (14.3%)	2243/16102 (13.9%)	RR 0.98 (0.91 to 1.04)	143 per 1000	3 fewer per 1000 (from 13 fewer to 6 more)
Death											
32215 (6 RCTs)	not serious	not serious	not serious	not serious	none	⊕⊕⊕⊕ High	761/16113 (4.7%)	712/16102 (4.4%)	RR 0.93 (0.85 to 1.03)	47 per 1000	3 fewer per 1000 (from 7 fewer to 1 more)
pIMD											
32098 (6 RCTs)	not serious	not serious	not serious	not serious	none	⊕⊕⊕⊕ High	207/16113 (1.3%)	190/15985 (1.2%)	RR 0.92 (0.76 to 1.12)	13 per 1000	1 fewer per 1000 (from 3 fewer to 2 more)

CI: confidence interval; RR: risk ratio

Table 24 – Serious adverse events, fatal adverse events and PIMD in immunocompromised individuals

Study	Serious adverse events				Fatal adverse events				pIMD			
	RZV		Placebo		RZV		Placebo		RZV		Placebo	
	n/N	% (95% CI)	n/N	% (95% CI)	n/N	% (95% CI)	n/N	% (95% CI)	n/N	% (95% CI)	n/N	% (95% CI)
Zoster-002	263/922	28.5	241/924	26.1	77/922	8.4	79/924	8.5	13/922	1.4	8/924	0.9
ZOE-HSCT⁶⁹		(25.6-31.6)		(23.3-29)		(6.6-10.3)		(6.8-10.5)		(0.8-2.4)		(0.4-1.7)
Zoster-028⁷⁰	46/117	39.3	45/115	39.1	12/117	10.3	11/115	9.6	0	0	1/115	0.9
Solid Tumour		(30.4-48.8)		(30.2-48.7)		(5.4-17.2)		(4.9-16.5)				
Zoster-039	66/283	23.3	82/279	29.4	29/283	10.2	37/279	13.3	3/283	1.1	2/279	0.7
Haematological Malignancies⁷¹		(18.5-28.7)		(24.1-35.1)		(7.0-14.4)		(9.5-17.8)		(0.2-3.1)		(0.1-2.6)
Zoster-041⁷²	26/132	19.7	33/132	25.0	1/132	0.8	1/132	0.8	4/132	3.0	2/132	1.5
Renal Transplant		(13.3-27.5)		(17.9-33.3)						(0.8-7.6)		(0.2-5.4)

CI: confidence interval, n: number of events, N: number of participants, pIMD: potential immune-mediated diseases, RZV = recombinant zoster vaccine


Table 25 – Vaccine effectiveness in real world (data from observational studies), per age-group

Study	Patients	FU	RZV % PY (n/T)	C% PY (n/T)	Unadjusted Vaccine Effectiveness (95 % CI)	Adjusted Vaccine Effectiveness (95 % CI)
OLDW USA⁷⁴	≥ 50 years, not IC Retrospective cohort	7m	2.6 (298/115 125)	8.9 (64 169/7 184 911)	68.3 (64.4-71.7)	85.5 (83.5-87.3)
	50-59y		<5.4 (<11/2019)	6.8 (15 424/2 252 215)	74.3 (20.3-91.7)	85.6 (53.3-95.6)
	60-69y		>1.5 (>34/22 934)	8.5 (1726/2 040 881)	75.5 (66.8-81.9)	87.7 (82.5-91.4)
	70-79y		2.5 (161/65 423)	10.3 (19 920/1 926 358)	69.4 (64.3-73.8)	86.5 (83.9-88.6)
	≥80y		3.7 (92/24 750)	11.9 (11 499/965 456)	60.2 (51.1-67.6)	80.3 (75.1-84.3)
	Male		1.9 (92/48 288)	7.1 (24 142/3 422 927)	71.9 (65.5-77.1)	86.8 (88.3-89.6)
	Female		3.1 (206/66 458)	10.6 (39 977/3 757 202)	66.6 (61.7-70.9)	84.7 (82.2-87.0)
KPH USA⁷⁵	≥ 50 years, not IC Retrospective cohort	730 d	3.3 (27/8291)	10.6 (1.273/119 719)	73.8 (60.7-82.5)	83.5 (74.9-89.2)
	50-59y		0 (0/196)	9.4 (467/49 449)	100	100
	60-69y		5.6 (4/717)	10.4 (442/42 592)	48.0 (-40.7-80.8)	67.7 (11.8-88.1)
	70-79y		2.9 (13/4537)	11.9 (214/17 914)	73.0 (51.8-84.9)	83.3 (70.1-90.7)
	≥80y		3.5 (10/2841)	15.4 (150/9764)	78.3 (58.1-88.8)	86.4 (73.5-93.0)
	Male		2.1 (8/3799)	9.1 (533/58 334)	80.6 (60.8-90.4)	89.3 (77.9-94.8)
	Female		4.2 (19/4492)	12.1 (740/61 386)	68.5 (48.5-80.8)	79.5 (66.0-87.7)
Medicare USA⁷⁶	≥ 65 years; Prospective cohort	7.1 m	3.1 (1880/609 000)	10.3 (258 293/25 026 026)	70.1 (68.6-71.5)	
	65-79y		3.0 (1473/495 000)	10.1 (191 424/18 962 000)	70.6 (68.9-72.1)	
	≥80y		3.6 (407/114 000)	11.0 (66 869/6 064 000)	68.5 (65.1-71.6)	
	Not immuno-compromised		3.0 (1737/584 000)	10.0 (239 789/23 947 000)	70.5 (69.0-72.0)	
	Immuno-compromised		5.9 (143/24 000)	17.2 (18 504/1 079 000)	64.1 (57.2-69.8)	
	Auto-immune disease		4.4 (167/38 000)	14.9 (20 640/1 387 000)	68.0 (62.3-72.8)	
VAHS USA⁸¹	≥ 50 years; patients with IBD Retrospective cohort	1.13y				
	50-60y		0 (0/716)	3.9 (69/17 561)	100	
	≥60y		1.8 (8/4445)	4.6 (268/58 663)	60.6 (20.5-80.5)	

OLDW OptumLabs Data Warehouse, KPH Kaiser Permanente Hawaii, VAHS Veterans Affairs Healthcare system, PY person-years, n = number of cases, FU follow-up; OLDW adjusted for age, sex, race, region, prior zoster vaccine live, antiviral use, healthcare utilization and Charlson comorbidity index and KPH adjusted for sex, race, ethnicity, vaccination with ZVL in the one year before the index date, age, healthcare utilisation, Deyo comorbidity index and systematic antiviral use



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