An analysis of spontaneously reported data of vesicular and bullous cutaneous eruptions occurring following vaccination with the adjuvanted recombinant zoster vaccine

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ESM 1 Definition of serious adverse events as defined by the International Conference on Harmonisation [1].

A serious adverse event was defined as any medical event that:

- resulted in death,
- was life-threatening,
- resulted in persistent or significant disability/incapacity,
- required in-patient hospitalization or prolonged existing hospitalization, or
- was a congenital anomaly/birth defect.

Reference

1. International Conference on Harmonisation. Topic E2A: Clinical safety data management: Definitions and standards for expedited reporting. 1994. https://database.ich.org/sites/default/files/E2A_Guideline.pdf. Accessed 25 August 2020.

ESM 2 Medical Dictionary for Regulatory Activities (MedDRA®) Preferred Terms (general and specific for the adjuvanted recombinant zoster vaccine) used to identify adverse event reports suggestive of lack of efficacy following vaccination with the adjuvanted recombinant zoster vaccine

Absence of immediate treatment response, atypical dose response relationship, device defective, device effect decreased, device effect delayed, device effect incomplete, device effect variable, device failure, device ineffective, device ineffective shock delivery, diet failure, drug half-life reduced, drug ineffective, drug ineffective for unapproved indication, drug level abnormal, drug level decreased, drug resistance, drug specific antibody present, drug tolerance, drug tolerance increased, missing dose response relationship, multiple-drug resistance, paradoxical drug reaction, remission not achieved, tachyphylaxis, therapeutic product effect decreased, therapeutic product effect delayed, therapeutic product effect incomplete, therapeutic product effect variable, therapeutic product effect ineffective, therapeutic product effect ineffective for unapproved indication, therapeutic reaction time decreased, therapeutic response changed, therapeutic response decreased, therapeutic response delayed, therapeutic response shortened, therapy non-responder, therapy partial responder, treatment failure, vaccination failure, virologic failure, disseminated varicella zoster vaccine virus infection, genital herpes zoster, herpes zoster, herpes zoster cutaneous disseminated, herpes zoster disseminated, herpes zoster infection neurological, herpes zoster meningitis, herpes zoster meningoencephalitis, herpes zoster meningomyelitis, herpes zoster meningoradiculitis, herpes zoster necrotising retinopathy, herpes zoster oticus, herpes zoster pharyngitis, lack of efficacy/effect, necrotising herpetic retinopathy, ophthalmic herpes zoster, post herpetic neuralgia, varicella zoster gastritis, varicella zoster oesophagitis, varicella zoster pneumonia, varicella zoster virus infection.

ESM 3 Medical Dictionary for Regulatory Activities (MedDRA®) Preferred Terms used to identify adverse event reports suggestive of other (non-herpes zoster) vesicular and bullous cutaneous eruptions following vaccination with the adjuvanted recombinant zoster vaccine

Acne pustular, acute generalised exanthematous pustulosis, blister, blister infected, blister rupture, blood blister, dermatitis bullous, dermatitis herpetiformis, erythema multiforme, genital blister, genital herpes, genital herpes simplex, gingival blister, herpes dermatitis, herpes oesophagitis, herpes ophthalmic, herpes simplex, herpes simplex encephalitis, herpes simplex reactivation, herpes virus infection, impetigo, injection site pustule, injection site vesicles, lip blister, meningoencephalitis herpetic, mucosa vesicle, nasal herpes, ophthalmic herpes simplex, oral herpes, oral mucosal blistering, oral pustule, oropharyngeal blistering, pemphigoid, pemphigus, pustule, rash pustular, rash vesicular, Stevens-Johnson syndrome, subcorneal pustular dermatosis, tongue blistering, vaginal mucosal blistering, varicella, varicella post vaccine.

ESM 4 Age- (and sex-)stratified background HZ incidence rates in the general population based on systematic literature reviews of epidemiological studies

Reference	Country	Study period	Sex	Age category (years)	IR per 1,000 PYs
[1]	France (as a proxy for Germany)	2005–2008	All	45–54	4.16
				55–64	5.77
				65–74	8.68
				75–84	9.85
				85–94	10.77
				95+	14.37
[2]	Germany	2007–2008	Female	50–54	7.80
				55–59	9.31
				60–64	10.59
				65–69	12.30
				70–74	12.59
				75–79	13.02
				80–84	13.15
				85–89	12.91
				90+	13.58
			Male	50–54	4.64
				55–59	5.84
				60–64	7.22
				65–69	8.95
				70–74	9.87
				75–79	10.96
				80–84	11.35
				85–89	11.65
				90+	11.99
[3]	USA	2011	All	50–59	6.74
				60–69	9.32
				70–79	12.02
				80+	12.78
[4]	Canada	1992–2010	All	50–59	4.55
				60–69	6.44
				70–79	8.26
				80+	8.41

IR, incidence rate; PY, person year; USA, United States of America.

References

1. Gonzalez Chiappe S, Sarazin M, Turbelin C, Lasserre A, Pelat C, Bonmarin I et al. Herpes zoster: Burden of disease in France. Vaccine. 2010; https://doi.org/10.1016/j.vaccine.2010.09.074.

2. Ultsch B, Siedler A, Rieck T, Reinhold T, Krause G, Wichmann O. Herpes zoster in Germany: Quantifying the burder of disease. BMC Infect Dis. 2011; https://doi.org/10.1186/1471-2334-11-173.

3. Johnson BH, Palmer L, Gatwood J, Lenhart G, Kawai K, Acosta CJ. Annual incidence rates of herpes zoster among an immunocompetent population in the United States. BMC Infect Dis. 2015; https://doi.org/10.1186/s12879-015-1262-8.

4. Tanuseputro P, Zagorski B, Chan KJ, Kwong JC. Population-based incidence of herpes zoster after introduction of a publicly funded varicella vaccination program. Vaccine. 2011; https://doi.org/10.1016/j.vaccine.2011.09.024.

ESM 5 Summary of the reports of adverse events suggestive of HZ or HZ complications retrieved using the MedDRA® PTs indicative of lack of efficacy (described in **ESM 2**)

	Total (N=2,465)	**Serious** (N=813)	**Non-serious** (N=1,652)
Not related to LoE[a]			
Total	42	10	32
HZ or HZ complications[b]			
Total	2,423	803	1,620
TTO unknown	832	478	354
TTO <30 days[c]	1,096	118	978
TTO 0–7 days	645	67	578
TTO 8–29 days	318	41	277
TTO <30 days; unspecified	133	10	123
TTO ≥30 days[d]	495	207	288

HZ, herpes zoster; LoE, lack of efficacy; MedDRA®, Medical Dictionary for Regulatory Activities; N, total number of reports in a given category; PT, Preferred Term; TTO, time-to-onset.

[a] Includes reports of varicella zoster virus infection, device failure only, or vaccination failure cases reported for a co-administered vaccine; [b] Includes post-herpetic neuralgia, ophthalmic HZ, disseminated cutaneous HZ, disseminated HZ, HZ oticus, or neurological HZ infection; [c] Includes reports with onset from day 0 to day 29 post-vaccination; [d] Includes reports with onset later than day 29 post-vaccination.

ESM 6 Other (non-herpes zoster) vesicular and bullous cutaneous eruptions identified with the search using the MedDRA® PTs indicative of other vesicular and bullous cutaneous eruptions (described in **ESM 3**), that contained sufficient information for assessment and were classified as injection site eruptions based on medical review of the case narrative

PT	**Number of reports**[a] (N=74)	**Number of serious reports**[a] (N=3)
Injection site vesicles	33	1
Blister	25	1
Rash vesicular	19	1
Injection site pustule	3	0
Pustule	2	2
Blister rupture	2	0

MedDRA®, Medical Dictionary for Regulatory Activities; N, total number of reports in a given category; PT, Preferred Term.

[a] One report could contain more than one AE reported by the same individual.

ESM 7 Description of reports of adverse events suggestive of non-herpes zoster vesicular and bullous cutaneous eruptions that were reported in the context of potential immune-mediated disease diagnoses for which insufficient information was available for full assessment

Among the 11 cases reported in the context of autoimmune bullous skin diseases, the majority (n=8) contained no details about the individual or the event (i.e., time-to-onset, clinical symptoms, skin biopsy, treatment); therefore, these reports were considered clinically unevaluable. The remaining three reports did not contain sufficient information to meet the diagnostic criteria for pemphigus or bullous pemphigoid [1] and alternative causes such as co-administered drugs, viral infections, and genetic predisposition could not be excluded during medical review; however, insufficient information for disease ascertainment was available. Among the three cases reported in the context of Stevens-Johnson syndrome (SJS), the information provided was insufficient for full assessment in one report and assessment of causal relationship with vaccination was confounded by a co-administered drug. In the remaining two reports, the GSK medical reviewer considered the event description, the relatively benign evolution of the symptoms, and the ambulatory treatment incompatible with SJS. Among the two cases reported in the context of erythema multiforme, one report contained insufficient information for further assessment. The other individual presented with the disease 21 days after co-administration of a first dose of the adjuvanted recombinant zoster vaccine (*Shingrix*, GSK, Belgium) with the combined hepatitis AB vaccine (*Twinrix*, GSK, Belgium).

Reference

1. Kershenovich R, Hodak E, Mimouni D. Diagnosis and classification of pemphigus and bullous pemphigoid. Autoimmun Rev. 2014; http://doi.org/10.1016/j.autrev.2014.01.011.

Trademark statement: *Shingrix* and *Twinrix* are trademarks owned by or licensed to the GSK group of companies.

ESM 8 Observed and expected incidences of possible varicella zoster virus reactivations within 30 days (day 0–day 29; main analysis) or 22 days (day 8–day 29; sensitivity analysis) post-vaccination with the adjuvanted recombinant zoster vaccine (reporting fraction of 75%)

Country/ Region	**Background IR**[a] [reference]	**Doses sold**	**Expected cases main analysis**[a]	**Expected cases sensitivity analysis**[a]	**Reported cases main analysis**	**Reported cases sensitivity analysis**	**Observed cases main analysis** (95% CI)	**Observed cases sensitivity analysis** (95% CI)
Canada	6.33 [1]	2,170,178	1,129	828	623	120	831 (767–899)	160 (133–191)
Germany	10.63 [2]	1,045,785	913	670	336	128	448 (401–499)	171 (142–203)
Germany (France[b])	7.67 [3]	1,045,785	658	483	336	128	448 (401–499)	171 (142–203)
USA	9.89 [4]	29,380,658	23,867	17,502	964	256	1,285 (1,205–1,369)	341 (301–386)
Worldwide								
	6.71 [1]	32,597,779	17,966	13,175	1,928	528	2,571 (2,457–2,688)	704 (645–767)
	9.82 [4]		26,289	19,279				
	10.39 [2]		27,830	20,409				
	7.53 [3]		20,164	14,787				

CI, confidence interval; IR, incidence rate; USA, United States of America.

[a] Background incidence rates in the general population and adjusted for the age distribution of recipients of the adjuvanted recombinant zoster vaccine; [b] Used as a proxy for Germany.

References

1. Tanuseputro P, Zagorski B, Chan KJ, Kwong JC. Population-based incidence of herpes zoster after introduction of a publicly funded varicella vaccination program. Vaccine. 2011; https://doi.org/10.1016/j.vaccine.2011.09.024.

2. Ultsch B, Siedler A, Rieck T, Reinhold T, Krause G, Wichmann O. Herpes zoster in Germany: Quantifying the burder of disease. BMC Infect Dis. 2011; https://doi.org/10.1186/1471-2334-11-173.

3. Gonzalez Chiappe S, Sarazin M, Turbelin C, Lasserre A, Pelat C, Bonmarin I et al. Herpes zoster: Burden of disease in France. Vaccine. 2010; https://doi.org/10.1016/j.vaccine.2010.09.074.

4. Johnson BH, Palmer L, Gatwood J, Lenhart G, Kawai K, Acosta CJ. Annual incidence rates of herpes zoster among an immunocompetent population in the United States. BMC Infect Dis. 2015; https://doi.org/10.1186/s12879-015-1262-8.

ESM 9 Observed and expected incidences of possible varicella zoster virus reactivations within 30 days (day 0–day 29; main analysis) post-vaccination with the adjuvanted recombinant zoster vaccine (reporting fractions of 25% and 50%)

Country/Region	**Background IR**[a] [reference]	**Doses sold**	**Expected cases**[a]	**Reported cases**	**Reporting fraction**	**Observed cases** (95% CI)
Canada						
	6.33 [1]	2,170,178	1,129	623	0.25	2,492 (2,300–2,696)
					0.5	1,246 (1,150–1,348)
Germany						
	10.63 [2]	1,045,785	913	336	0.25	1,344 (1,204–1,496)
					0.5	672 (602–748)
	7.67 [3]	1,045,785	658	336	0.25	1,344 (1,204–1,496)
					0.5	672 (602–748)
USA						
	9.89 [4]	29,380,658	23,867	964	0.25	3,856 (3,616–4,107)
					0.5	1,928 (1,808–2,054)
Worldwide						
	6.71 [1]	32,597,779	17,966	1,928	0.25	7,712 (7,372–8,064)
					0.5	3,856 (3,686–4,032)
	9.82 [4]	32,597,779	26,289	1,928	0.25	7,712 (7,372–8,064)
					0.5	3,856 (3,686–4,032)
	10.39 [2]	32,597,779	27,830	1,928	0.25	7,712 (7,372–8,064)
					0.5	3,856 (3,686–4,032)
	7.53 [3]	32,597,779	20,164	1,928	0.25	7,712 (7,372–8,064)
					0.5	3,856 (3,686–4,032)

IR, incidence rate; USA, United States of America; 95% CI, 95% confidence interval.

[a] Background incidence rates in the general population and adjusted for the age distribution of recipients of the adjuvanted recombinant zoster vaccine.

References

1. Tanuseputro P, Zagorski B, Chan KJ, Kwong JC. Population-based incidence of herpes zoster after introduction of a publicly funded varicella vaccination program. Vaccine. 2011; https://doi.org/10.1016/j.vaccine.2011.09.024.

2. Ultsch B, Siedler A, Rieck T, Reinhold T, Krause G, Wichmann O. Herpes zoster in Germany: Quantifying the burder of disease. BMC Infect Dis. 2011; https://doi.org/10.1186/1471-2334-11-173.

3. Gonzalez Chiappe S, Sarazin M, Turbelin C, Lasserre A, Pelat C, Bonmarin I et al. Herpes zoster: Burden of disease in France. Vaccine. 2010; https://doi.org/10.1016/j.vaccine.2010.09.074.

4. Johnson BH, Palmer L, Gatwood J, Lenhart G, Kawai K, Acosta CJ. Annual incidence rates of herpes zoster among an immunocompetent population in the United States. BMC Infect Dis. 2015; https://doi.org/10.1186/s12879-015-1262-8.

ESM 10 Observed and expected incidences of possible varicella zoster virus reactivations within 22 days (day 8–day 29; sensitivity analysis) post-vaccination with the adjuvanted recombinant zoster vaccine (reporting fractions of 25% and 50%)

Country/Region	**Background IR**[a] [reference]	**Doses sold**	**Expected cases**[a]	**Reported cases**	**Reporting fraction**	**Observed cases** (95% CI)
Canada						
	6.33 [1]	2,170,178	828	120	0.25	480 (398–574)
					0.5	240 (199–287)
Germany						
	10.63 [2]	1,045,785	670	128	0.25	512 (427–609)
					0.5	256 (214–304)
	7.67 [3]	1,045,785	483	128	0.25	512 (427–609)
					0.5	256 (214–304)
USA						
	9.89 [4]	29,380,658	17,502	256	0.25	1,024 (902–1,157)
					0.5	512 (451–579)
Worldwide						
	6.71 [1]	32,597,779	13,175	528	0.25	2,112 (1,936–2,300)
					0.5	1,056 (968–1,150)
	9.82 [4]	32,597,779	19,279	528	0.25	2,112 (1,936–2,300)
					0.5	1,056 (968–1,150)
	10.39 [2]	32,597,779	20,409	528	0.25	2,112 (1,936–2,300)
					0.5	1,056 (968–1,150)
	7.53 [3]	32,597,779	14,787	528	0.25	2,112 (1,936–2,300)
					0.5	1,056 (968–1,150)

IR, incidence rate; USA, United States of America; 95% CI, 95% confidence interval.

[a] Background incidence rates in the general population and adjusted for the age distribution of recipients of the adjuvanted recombinant zoster vaccine.

References

1. Tanuseputro P, Zagorski B, Chan KJ, Kwong JC. Population-based incidence of herpes zoster after introduction of a publicly funded varicella vaccination program. Vaccine. 2011; https://doi.org/10.1016/j.vaccine.2011.09.024.

2. Ultsch B, Siedler A, Rieck T, Reinhold T, Krause G, Wichmann O. Herpes zoster in Germany: Quantifying the burder of disease. BMC Infect Dis. 2011; https://doi.org/10.1186/1471-2334-11-173.

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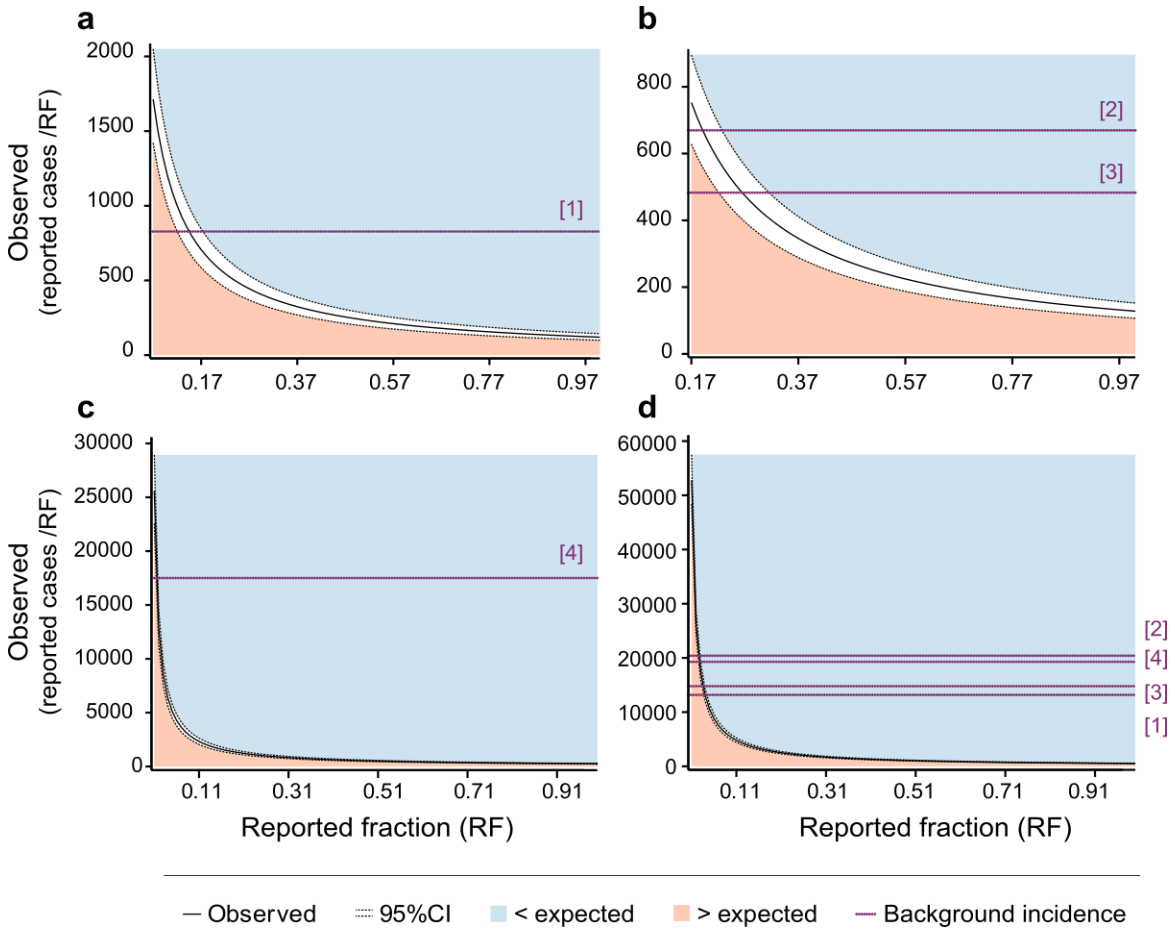
4. Johnson BH, Palmer L, Gatwood J, Lenhart G, Kawai K, Acosta CJ. Annual incidence rates of herpes zoster among an immunocompetent population in the United States. BMC Infect Dis. 2015; https://doi.org/10.1186/s12879-015-1262-8.

ESM 11 Significance area for the equality test of observed and expected incidences of herpes zoster within 22 days (day 8–day 29) after vaccination with the adjuvanted recombinant zoster vaccine in Canada (a), Germany (b), the United States of America (c), and worldwide (d)



CI, confidence interval.

Number of doses distributed was 2,170,178 for Canada, 1,045,785 for Germany, 29,380,658 for the United States of America, and 32,597,779 for worldwide; Background incidence represents the herpes zoster incidence rate in the general population and is adjusted for the age distribution of recipients of the adjuvanted recombinant zoster vaccine.

References

1. Tanuseputro P, Zagorski B, Chan KJ, Kwong JC. Population-based incidence of herpes zoster after introduction of a publicly funded varicella vaccination program. Vaccine. 2011; https://doi.org/10.1016/j.vaccine.2011.09.024.

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