//Suspected cases of herpes zoster and pronounced skin reactions associated with vaccination against herpes zoster and postherpetic neuralgia: results of an observational study in individuals vaccinated with Shingrix in Germany//

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The Paul-Ehrlich-Institut, whose remit includes the safety of vaccines in Germany, received numerous suspected case reports in 2019 of a herpes zoster-like skin manifestation after administration of Shingrix, an adjuvanted recombinant vaccine against herpes zoster and postherpetic neuralgia. Shingrix has been authorised since 2018. In 2020, the Paul-Ehrlich-Institut initiated an observational study to clarify whether these are cases of herpes zoster. Data on pre-existing and concomitant conditions, relevant previous and concomitant medications, Shingrix vaccination, and skin appearance were collected as part of this study. In addition, photo documentation of the skin manifestation was created and swabs were taken from the skin lesion. The German Consulting Laboratory for Herpes Simplex Virus and Varicella Zoster Virus, University Medical Center Freiburg, examined the samples taken by means of PCR and genotyping. Two dermatologists independently validated the recruited suspected cases on the basis of the case documentation, the photographic material and the virological findings. A third dermatologist also validated the cases in which the two independently created validations differed from each other. The results of the observational study were published in the EUROSURVEILLANCE journal.[1] They are briefly summarised in the following article.

INTRODUCTION

Individuals whose medical history includes chickenpox (varicella) caused by primary infection with the varicella-zoster virus (VZV) (Figure 1) may develop shingles (herpes zoster, HZ) at some point in their life through the endogenous reactivation of VZV.[2]

Vaccination can prevent both HZ, which is characterised by a painful skin manifestation with blisters, and postherpetic neuralgia (PHN), a complication of HZ.[3]

Shingrix (GlaxoSmithKline Biologicals S.A., Rixensart, Belgium) is a recombinant subunit vaccine for the prevention of HZ and PHN. It was authorised in the EU in March 2018.[4]

Germany's Standing Committee on Vaccination recommends that all persons aged 60 and over and persons aged 50 and over with certain underlying conditions or immunodeficiencies receive two doses of Shingrix at intervals of at least two months to a maximum of six months.

By the end of 2019, the Drug Commission of the German Medical Association and the Paul-Ehrlich-Institut had received numerous suspected case reports of HZ and of pronounced, sometimes bullous skin reactions in close temporal association with Shingrix vaccination (Figure 2).[5]

As the competent higher federal authority for the safety of vaccines in Germany, the Paul-Ehrlich-Institut initiated a multicentre observational study in April 2020 to investigate whether the skin symptoms that occurred shortly after administration of one or more doses of Shingrix were HZ episodes that were possible vaccination complications.[6]

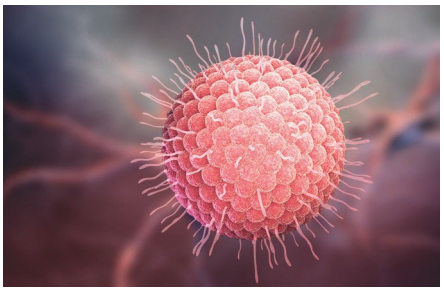


Figure 1 (left): Varicella-zoster virus
Source: Tatiana Shepeleva/ Shutterstock

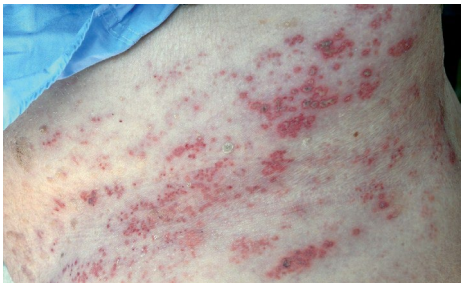


Figure 2 (right): Study patient with shingles

METHODS

Suspected cases of damage to health beyond the usual extent of a vaccination reaction that were reported to the Paul-Ehrlich-Institut from 15 April to 14 October, 2020, pursuant to division 3 section 6 subsection 1 no. 3 of the Infection Protection Act,[7] had to meet the following inclusion criteria in order to be included in the observational study:

- suspected case of HZ or HZ-like skin manifestation,
- symptom onset within 28 days of Shingrix vaccination,
- sufficiently informative physician's report on the suspected adverse event following immunisation (AEFI).[8]

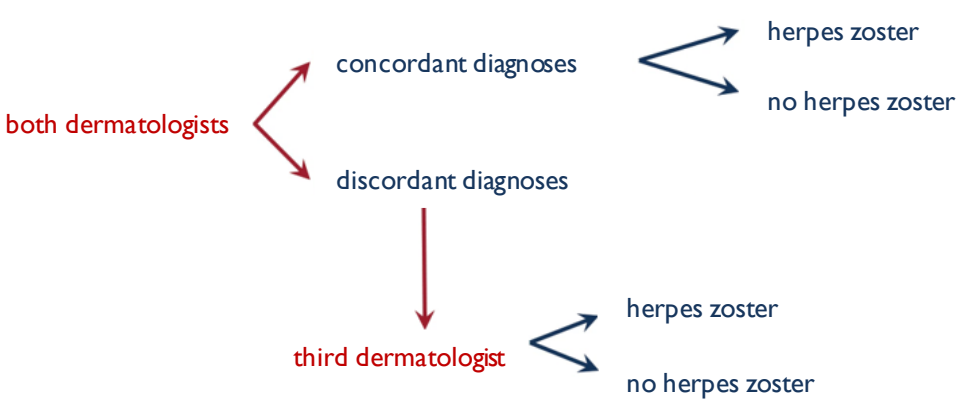
The prerequisite for participation in the observational study was written consent from the patient and the physician.

Data on pre-existing and concomitant conditions, relevant previous and concomitant medications, HZ vaccination, and skin appearance were collected as part of the study. Photos were taken to document the skin manifestation and swabs were taken from the skin lesion (eSwab, Copan Liquid Amies Elution Swab, Copan Italia S.p.A., Brescia, Italy).[9]

A PCR examination was carried out for the detection of VZV and herpes simplex virus (HSV) DNA.[10] In the case of a positive VZV laboratory finding, genotyping was also carried out to distinguish between vaccine and wild-type.[11]

Two dermatologists independently validated the cases (Figure 3). If the two evaluations differed from each other, the cases underwent an additional examination by a third dermatologist.

Figure 3: Case validation



All collected data was pseudonymised in a FileMaker Pro database (Claris International Inc., Santa Clara, United States, version 18.0.3). The statistical analysis was carried out with SAS (Statistical Analysis System, SAS Institute Inc., Cary, United States, version 9.4).

RESULTS

The Paul-Ehrlich-Institut received 96 requests to participate in the study within the six-month recruitment phase from all over Germany.

After a screening process, a total of 80 suspected cases were included in the observational study, 27 of which tested positive for VZV by PCR test. All of those positive VZV cases were genotyped as wild type (Table 1). Two of the 53 VZV-negative samples tested positive for HSV-1 by PCR test and five tested positive for HSV-2. Eight were excluded from the analysis because the sample had not been taken within 14 days of the onset of symptoms and thus there was reason to doubt the negative PCR result.

The study population was predominantly female (62.5%) and a majority of patients were between 60 and 69 years old (45.8%). The thoracic (44.4%) and cervical (37.5%) dermatomes were the most commonly affected. Regardless of the PCR finding and whether it was after the first or second dose of Shingrix, 48 patients (66.7%) experienced symptoms within the first week and less frequently in the second, third, and fourth weeks after administration of the vaccine.

Among the suspected AEFI, four hospitalisations and two cases of disabling, long-lasting or potentially irreversible medical conditions (PHN with severe pain in both cases) were reported. These AEFI were defined as serious in accordance with section 4 subsection 13 of the Medicinal Products Act.[12] The majority of cases had no history of HZ episodes (68.1%) or of immunosuppression or immunodeficiency (82.4%). The use of immunosuppressive/immunomodulatory medicinal products in temporal association to administration of Shingrix was reported in seven cases (9.7%).

In half of the cases (n = 26/52), the HZ/varicella diagnosis reported by the treating physician was not confirmed (Table 2). The administration of antivirals was reported in eight of the 45 VZV-negative cases, but only two of these eight patients tested HSV-positive.

Two dermatologists independently confirmed the HZ diagnosis in 25 of the 27 VZV-positive cases. One of the two remaining cases was diagnosed as HZ by the third dermatologist, while the other was classified as "not assessable" due to the lack of photo documentation.

In the 45 VZV-negative cases, HSV was the most common (n = 9) concordant differential diagnosis documented by the two dermatologists, followed by exanthema (n = 2), eczema (n = 2), and folliculitis (n = 1). The two dermatologists questioned the PCR result in two of the 45 VZV-negative cases. Both cases could not be validated by the third dermatologist due to lack of information.

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Table 1: Case characteristics

		cases analysed		VZV-positive cases		VZV-negative cases		VZV-positive vs. VZV-negative
		n	%	n	%	n	%	p value
total		*72*	*100.0*	*27*	*100.0*	*45*	*100.0*	
gender (of patients)	male	27	37.5	9	33.3	18	40.0	0.572
	female	45	62.5	18	66.7	27	60.0	
age (of patients)	≤49	1	1.4	0	0.0	1	2.2	–
	50–59	8	11.1	3	11.1	5	11.1	
	60–69	33	45.8	10	37.0	23	51.1	
	70–79	23	31.9	10	37.0	13	28.9	
	80–89	7	9.7	4	14.8	3	6.7	
symptom location (dermatomes)	cervical	27	37.5	5	18.5	22	48.9	0.010**
	thoracic	32	44.4	13	48.2	19	42.2	0.624
	lumbar	12	16.7	7	25.9	5	11.1	0.117
	sacral	10	13.9	4	14.8	6	13.3	1.000
symptom onset (day/s after vaccination)	0–7	48	66.7	20	74.1	28	62.2	0.302
	8–28	24	33.3	7	25.9	17	37.8	
symptom onset (day/s after dose 1)	0–7	31	62.0	15	71.4	16	55.2	–
	8–14	12	24.0	3	14.3	9	31.0	
	15–21	6	12.0	2	9.5	4	13.8	
	22–28	1	2.0	1	4.8	0	0.0	
symptom onset (day/s after dose 2)	0–7	17	77.3	5	83.3	12	75.0	–
	8–14	3	13.6	1	16.7	2	12.5	
	15–21	0	0.0	0	0.0	0	0.0	
	22–28	2	9.1	0	0.0	2	12.5	
previous HZ (number of episodes)	at least 1	22	31.9	5	20.0	17	38.6	0.110
	1	13	18.8	4	16.0	9	20.5	–
	2–5	6	8.7	1	4.0	5	11.4	
	6–10	1	1.4	0	0.0	1	2.3	
	≥11	2	2.9	0	0.0	2	4.5	
	none	47	68.1	20	80.0	27	61.4	
immune disease	deficiency/ suppression	12	17.6	4	16.0	8	18.6	1.000
concomitant medication(s) (multiple answers possible)	other vaccination	2	2.8	1	3.7	1	2.2	1.000
	immune suppressant or modulator	7	9.7	2	7.4	5	11.1	0.704
	NSAIDs*	17	23.6	6	22.2	11	24.4	0.830
antiviral therapy	Aciclovir/ Brivudine	19	26.4	11	40.7	8	17.8	0.032**

*non-steroidal anti-inflammatory drugs

**statistically significant

Table 2: Case diagnostics

					cases analysed		VZV-positive cases		VZV-negative cases	
					n	%	n	%	n	%
total					***72***	***100.0***	***27***	***100.0***	***45***	***100.0***
treating physicians		HZ/varicella			52	72.2	26	96.3	26	57.8
		no HZ/varicella			20	27.8	1	3.7	19	42.2
both dermatologists	concordant diagnoses	HZ		classic	25	34.7	25	92.6	–	–
				disseminatus	0	0.0	0	0.0	–	–
				sine herpete	0	0.0	0	0.0	–	–
		no HZ	concordant differential diagnoses	HSV	9	12.5	–	–	9	20.0
				exanthema	2	2.8	–	–	2	4.4
				eczema	2	2.8	–	–	2	4.4
				folliculitis	1	1.4	–	–	1	2.2
			discordant differential diagnoses		29	40.3	–	–	29	64.4
	discordant diagnoses				4	5.5	2	7.4	2	4.4
(discordant diagnoses by the two dermatologists)				***subtotal***	***4***	***100.0***	***2***	***100.0***	***2***	***100.0***
third dermatologist	diagnoses	HZ			1	25.0	1	50.0	0	0.0
		no HZ			0	0.0	0	0.0	0	0.0
		not assessable			3	75.0	1	50.0	2	100.0

DISCUSSION

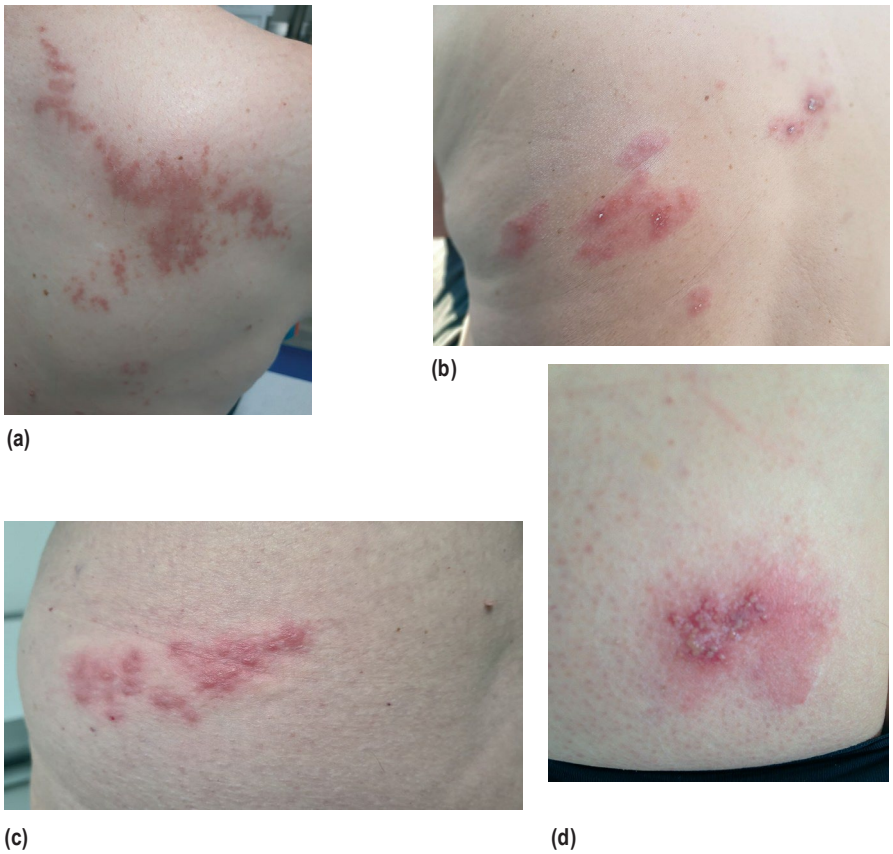
The Paul-Ehrlich-Institut conducted an observational study in Germany in order to conduct a closer analysis of the occurrence of HZ or HZ-like skin manifestations shortly after vaccination with Shingrix. The cases were recruited nationwide, so this multicentre case series well represents the German patient population with the exception of the very elderly (≥90 years). [13]

37.5 percent of the cases analysed were VZV-positive. The first symptoms occurred in the first few weeks after the first dose or immediately after the second dose of Shingrix, which means they occurred before the vaccination protection provided by the vaccination series was complete.[14, 15] The wild-type strain was detected in all VZV-positive samples. The detection of only the wild-type strain was consistent with the fact that no patient had previously been vaccinated with the live vaccine Zostavax.[16]

62.5 percent of the cases analysed were VZV-negative. The most common concordant differential diagnoses by the dermatologists were HSV, exanthema, eczema, and folliculitis. This observational study shows how difficult it is to distinguish shingles from other skin manifestations without a PCR test for VZV (Figure 4).

Observational study strengths

The observational study was characterised by the use of objective methods via VZV/HSV PCR tests of skin lesions and dermatological case validations.



(a) (b) (c) (d)

Figure 4:
Study cases that were PCR negative (a) or positive for VZV (b), HSV-1 (c) and HSV-2 (d)

The patients included in the study benefited from the virological examinations that helped treating physicians to choose the appropriate treatment, e.g. use of antivirals in the event of a positive PCR result or discontinuation of antivirals in the event of a negative PCR result.

Observational study limitations

The result of the PCR test and dermatological validation could have been influenced by improper sample collection or handing or incomplete case documentation, respectively.

CONCLUSION

Herpes zoster (shingles) is a common condition caused by the varicella-zoster virus. Affected patients suffer from a painful skin eruption with blisters.

The wild-type strain was identified in all cases positive for varicella-zoster virus. Skin manifestations usually occurred in patients without complete vaccination protection.

The results of this observational study do not indicate a causal relationship, but only a temporal relationship with the Shingrix vaccination.

Currently, no measures are required to minimise the risk of adverse events following immunisation after administration of Shingrix.

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