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Final Report on analysis results

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1. Rationale and background

Inactivated varicella zoster vaccine is a vaccine indicated for prevention of herpes zoster and postherpetic neuralgia, in adults 50 years of age or older. It was centrally authorised in the EU on 21/03/2018. Virus reactivation in immunocompetent individuals with a history of herpes zoster constitutes an important potential risk included in the RMP. Since the launch of inactivated varicella zoster vaccine on the German market through to 15. September 2019, 181 suspected cases of herpes zoster like rash in close temporal association with the administration of inactivated varicella zoster vaccine were notified to German competent authorities. However, due to missing data and other limitations, spontaneous reporting does not provide reliable information whether only individuals with a history of herpes zoster are at risk of developing herpes zoster after immunisation with inactivated varicella zoster vaccine.

2. Research question and objectives

Is there an increased risk of herpes zoster following immunisation with inactivated varicella zoster vaccine as compared to another relevant inactivated vaccine, e.g. pneumococcal vaccine?

3. Research Methods

3.1. Study Design

The study design is descriptive, comparing a diagnosis of herpes zoster in patients with a first prescription for inactivated varicella zoster vaccine vs. patients with either a first prescription for pneumococcal vaccine (conjugated and unconjugated) or a first prescription for live attenuated varicella zoster vaccine, as two separate comparisons. Patients with a simultaneous first prescription for both types of vaccines (either inactivated varicella zoster vaccine and pneumococcal vaccine together or inactivated varicella zoster vaccine and live attenuated varicella zoster vaccine together) will not be included in the study. Patients must have a minimum observation time of 180 days prior to the first prescription and must have a minimum follow-up time of 28 days after the first prescription. Subsequent prescriptions will also be studied provided the patient has not yet received a prescription for the other vaccine and fulfils the requirement for a minimum follow-up time of 28 days after the prescription. An extended analysis up to 56 days after the prescription, requiring a minimum follow-up time of 56 days will also be performed as a sensitivity analysis.

3.2. Study period

1 March 2018 and 30 June 2019.

3.3. Database

IMS® Disease Analyzer Germany version June 2019

3.4. Data transformation

Events with a diagnosis certainty of 'condition after' will be considered as history of the condition and will not be collected as outcome events between 1-28 days after the vaccination. Events with a recorded diagnosis certainty of 'exclusion of' will also not be considered. Events with a diagnosis certainty provided as 'not specified', 'suspected' or 'confirmed' will be included. There will be a sensitivity analysis for zoster outcomes with a diagnosis certainty provided as 'confirmed'.

Results will be stratified by gender and age group (2-17, 18-29, 30-49, 50-59, 60-69, 70-79, 80-89 and 90-99 years). Results will also be stratified by immunodeficiency or immunosuppression

(together). Immunodeficiency will be defined as an ICD 10 code of B20-B24 (HIV), C81-C96 (Malignant neoplasms, stated or presumed to be primary, of lymphoid, haematopoietic and related tissue) or D80-D84 (Immunodeficiency diagnoses) up to the first vaccination prescription. Immunosuppression will be defined as a prescription for a medicinal product belonging to the WHO ATC codes L01 (antineoplastic agents) or L04 (immunosuppressants) within 90 days before and up to the first vaccination date. A separate analysis will also consider systemic corticosteroid use (WHO ATC code H02) as immunosuppressive treatment.

Results will be stratified by a prior history of varicella or herpes zoster (ICD 10 codes B01 and B02).

If a code suggestive of the vaccination date defined as an ICD 10 code of Z23 (Need for immunization against single bacterial diseases), Z24 (Need for immunization against certain single viral diseases), Z25 (Need for immunization against other single viral diseases), Z26 (Need for immunization against other single infectious diseases) or Z27 (Need for immunization against combinations of infectious diseases) is identified during the first 28 days after the vaccination prescription it will be considered to represent the vaccination date. A sensitivity analysis will include only those outcomes that are recorded either in the absence of a vaccination date or at least one day after a recorded vaccination date.

The age of the patient will be the age at the time of the vaccination prescription. The first prescription and any subsequent prescriptions will be considered separately.

Milestone	Date	Comments
Query request	11/11/2019	
Feasibility Feedback	03/12/2019	
Data analysis plan draft	06/01/2020	
Data analysis plan agreed	09/01/2020	
Data analysis start	13/01/2020	
Draft report of results	31/01/2020	
Final Report of results		
End of data collection		
Registration in the EU PAS register (indicate if applicable yes/no)		Analyses performed as part of the pilot will be published as part of the full report of the pilot an data analytics

3.5. Milestones

3.6. Study population

Definition of study population:

- Patients 2-99 years, both genders
- Disease codes:

- History of varicella: ICD 10 code B01 (includes events recorded 1-28 days after the vaccination prescription if the diagnosis certainty is 'condition after')
- History of herpes zoster: ICD 10 code B02 (includes events recorded 1-28 days after the vaccination prescription if the diagnosis certainty is 'condition after')
- History of immunodeficiency: ICD 10 codes B20-B24, C81-C96 or D80-D84
- Vaccination date: ICD 10 codes Z23-Z27
- Treatment codes:
 - Treatment with inactivated varicella zoster vaccine:
 - EphMRA ATC code J07E2, therapy name contains 'shingrix'
 - Treatment with live attenuated varicella zoster vaccine:
 - EphMRA ATC code J07E2, therapy name not contains 'shingrix'
 - Treatment with pneumococcal vaccine:
 - EphMRA ATC code J07D1:
 - Conjugated vaccine: Molecule name contains 'conjugated' or therapy name contains 'synflorix'
 - Unconjugated vaccine: Molecule name not contains `conjugated' and therapy name not contains `synflorix'
 - Prior immunosuppressive treatment within 90 days prior vaccination prescription:
 - EphMRA ATC code L01 and L04 (excluding L01X1 'mistletoe extracts')
 - Prior immunosuppressive treatment or systemic corticosteroid treatment within 90 days prior vaccination prescription:
 - EphMRA ATC code L01 L04 and H02 (excluding L01X1 'mistletoe extracts')
- Exclusion criteria applied: Patients are excluded in case of same day prescription for inactivated varicella zoster vaccine and either live attenuated varicella zoster vaccine or pneumococcal vaccine. Patients are required to have a minimum observation period of 180 days prior to the first vaccination prescription and at least 28 days of follow-up after the first vaccination prescription. A separate sensitivity analysis requires patients to have at least 56 days of follow-up.
- Other patient characteristics: Results are separated by age group and gender, by a history of immunodeficiency/immunosuppression, and by a history of varicella or zoster.
- Relevant time windows: Patients are followed up for 28 days after the vaccination prescription (56 days as a sensitivity analysis).

3.7. Exposure

- Definition of exposure:
 - Inactivated varicella zoster vaccine:
 - EphMRA ATC code J07E2 and therapy name contains 'shingrix'
 - Live attenuated varicella zoster vaccine

- EphMRA ATC code J07E2 and therapy name not contains 'shingrix'
- Pneumococcal vaccine:
 - EphMRA ATC code J07D1:
 - Conjugated vaccine (molecule name contains 'conjugated' or therapy name contains 'synflorix')
 - Unconjugated vaccine (molecule name not contains `conjugated' and therapy name not contains `synflorix')
- The patient is excluded if he/she receives a first prescription for inactivated varicella zoster vaccine on the same date as a first prescription for live attenuated varicella zoster vaccine or pneumococcal vaccine.

3.8. Outcome(s)

- Definition of medical events
 - Herpes zoster: ICD 10 code B02:
 - Events with a diagnosis certainty of 'exclusion of' and 'condition after' are excluded from the analysis
 - In a sensitivity analysis events with a diagnosis certainty of `confirmed' are presented separately

3.9. Analysis

- Details of Analysis (as planned and as applicable)
- Statistical Methods
 - Type of analysis: Descriptive cohort analysis
 - Measure of occurrence: Occurrence of herpes zoster 1-28 days after the vaccination prescription (1-56 as part of sensitivity analyses, see also below).
 - Measure of association: Comparative occurrence of herpes zoster in patients with a vaccination prescription for inactivated varicella zoster vaccine vs live attenuated varicella zoster vaccine and pneumococcal vaccine
 - Stratified analyses: Age group, gender, history of immunodeficiency/immunosuppression, history of varicella or zoster
 - Confounders (with codes): Not applicable
 - Statistical model: Descriptive analysis
 - Handling of missing data: Analysis of complete data.
 - Sensitivity analyses:
 - Results limited to events recorded after a prescription in case of no further code marking the vaccination date or events that occur after a recorded vaccination date through a code marking possible vaccination (e.g. Z23.8)(the full analysis only used the date of prescription and did not consider Z codes, if entered to ascertain the date of vaccination).

- \circ $\;$ Results limited to events with a diagnosis certainty of `confirmed' $\;$
- Follow up time extended to 56 days
- Separate analyses for subtypes of pneumococcal vaccines (conjugated and unconjugated)

The following additional analyses were also performed in addition to the analysis plan previously agreed:

- A separate analysis excluding events of post zoster neuralgia (ICD 10 code B02.2) and events where the medical event text mentioned prophylaxis (Vorbeugen)
- A separate analysis of prescriptions for systemic anti-herpes treatment (acyclovir, valaciclovir or famciclovir identified as molecule name equals 'aciclovir', valaciclovir' or 'famciclovir' and EphMRA ATC code includes 'J')

4. Results

4.1. Study period

The study period is between 1 March 2018 and 30 June 2019.

4.2. Database

The database is IMS® Disease Analyzer Germany.

4.3. Outcome(s)

For definition of medical events, please see section 3.8.

4.4. Analysis

For details of the analysis, please see section 3.9. Two additional analyses were performed in addition to the analyses specified in the analysis plan (see section 3.9 as well). The total number of patients with a prescription by quarter and type of vaccine is shown in the table below (please note that these counts deviate from the counts provided as parts of the analysis results due to required follow-up times, and other analysis specifications).

Time period for prescription	Live attenuated varicella zoster	Inactivated varicella zoster	Pneumococcal
2018 Q1	293	0	1184
2018 Q2	843	46	3132
2018 Q3	790	187	3231
2018 Q4	885	552	4730
2019 Q1	1266	1471	3167
2019 Q2	1352	3696	3132

4.5. Results of analysis

Immunodeficiency/immunosuppression will be referred to in the text as immunodeficiency.

Main summaries are presented in tables 1 and 2 including information on the number and frequency of events observed in patients receiving the different types of vaccines with and without history of immunodeficiency and with and without history of varicella zoster. Table 3 displays the distribution of included patients 2-99 years vs. patients of all ages for the different vaccines.

Inactivated varicella zoster vaccine versus live attenuated varicella zoster vaccine:

In patients without a history of immunodeficiency with no prior history of varicella zoster the frequency of herpes zoster events up to 28 days after the vaccination prescription was 5.5 (95% CI 3.1-9.8; 11/2010 patients) per 1000 patients receiving inactivated varicella zoster vaccination while no events were recorded in the group of patients receiving live attenuated varicella zoster vaccines (0/1163 patients). For the group of patients with a history of varicella zoster the corresponding frequency was 53.9 (95% CI 39.4-73.5) for inactivated varicella zoster vaccine and 31.7 (95% CI 8.7-108.6) for live attenuated varicella zoster vaccine. Most patients (78.6%) vaccinated with a prescription for live attenuated varicella zoster vaccine were 2 to 29 years of age whereas most patients (98.4%) vaccinated with inactivated varicella zoster vaccine were 30 years or older.

Within the smaller group of patients with a history of immunodeficiency, the number of recorded events resulted in a frequency of 11.1 (95% CI 3.1-39.6) per 1000 patients with no history of varicella zoster receiving inactivated varicella zoster vaccination, while no events were observed in 42 patients receiving live attenuated vaccines. For patients with history of varicella zoster, the frequency was 75.0 (95% CI 34.8-154.1) per 1000 in patients receiving inactivated varicels zoster vaccines no recorded events in five patients receiving live attenuated vaccines.

Inactivated varicella zoster vaccine versus pneumococcal vaccine

In patients without a history of immunodeficiency with no prior history of varicella zoster the frequency of herpes zoster events up to 28 days after the vaccination prescription was 5.5 (95% CI 3.0-10.1) per 1000 in patients receiving attenuated varicella zoster vaccination vs. 0.8 (95% CI 0.3-2.2) per 1000 in patients receiving pneumococcal vaccines . For the group of patients with a history of varicella zoster, corresponding frequencies were 55.5 (95% CI 40.5-75.5) per 1000 patients for inactivated varicella zoster vaccine and 3.4 (95% CI 0.6-19.2) per 1000 patients for pneumococcal vaccine.

Within the smaller group of patients with a history of immunodeficiency, the number of recorded events resulted in a frequency of 6.1 (95% CI 1.1-33.7) per 1000 patients in patients with no history of varicella zoster receiving inactivated varicella zoster vaccination, while no events were observed in 335 patients receiving pneumococcal vaccines. For patients with history of varicella zoster, the frequency was 76.9 (95% CI 35.7-157.8) per 1000 patients in patients receiving inactivated varicella zoster vaccines in patients receiving inactivated varicella zoster.

Those results indicate a slightly higher frequency of herpes zoster during 28 days of follow-up in patients receiving inactivated varicella zoster vaccines as compared to pneumococcal vaccines. A similar pattern is maintained in the subgroups of patients with and without history of immunodeficiency as well as in patients with and without history of varicella zoster, while the overall event rates in these risk groups seem to be higher. However, the subgroups of patients with risk factors is lower limiting also the interpretability of the results.

Overall these analyses are based on small number of events asking for very cautious interpretation of results.

Results split by age group and gender

The number of herpes zoster events within 1-28 days after the vaccination prescription by age group, gender and a history of varicella or zoster in patients with and without a history of immunodeficiency is shown in Tables 4 and 5 for the comparison between inactivated varicella zoster vaccine vs. live attenuated varicella zoster vaccine, and in Tables 6 and 7 for the comparison between inactivated varicella zoster vaccine vs. pneumococcal vaccine (results including corticosteroids are shown in Supplementary Tables S1 to S4). Results split also by type of pneumococcal vaccine (conjugated and unconjugated) are shown in Tables 8 and 9. Due to the overall very low number of events it is difficult to compare rates for the different types of pneumococcal vaccines. However, combining the different types of pneumococcal vaccines performed for the purpose of this rapid data analysis.

Results of analyses including only events reported in the absence of or after a recorded vaccination date are shown in Tables 10 to 13 (results including corticosteroids are shown in Supplementary Tables S5 to S8). Results limited to a diagnosis certainty of 'confirmed' are shown in Tables 14 and 15 (results including corticosteroids are shown in Supplementary Tables S9 and S10). Overall, results of these analyses show a similar picture as the main analysis albeit with a lower number of events and less precision.

In patients with a history of immunodeficiency reference is made to previous Tables 5 and 7 as all outcomes had a diagnosis certainty of 'confirmed'. Patients with a history of immunodeficiency seem to be experiencing more events of herpes zoster thereby constituting a risk factor. However, the number of events in this patient group is small not allowing for any firm conclusions.

Results in patients with and without immunodeficiency, excluding a diagnosis of post zoster neuralgia as well as medical event texts suggesting prophylaxis, are shown in Tables 16 to 19. Those additional analyses also yield the same pattern of results as the initial analysis.

Results of analyses with extended follow-up to 56 days in patients with and without immunodeficiency are provided in Tables 20 to 23. Results of these analyses show an increased proportion of patients with the outcome when the duration of follow-up is extended. However, these results have wider confidence limits due to the lower number of patients observable for as long as 56 days after the vaccination prescription compared to the shorter follow-up of 28 days. The loss of patients was particularly pronounced among patients with a prescription for inactivated varicella zoster vaccine, likely due to the increasing number of vaccinated patients towards the end of the study period for which available follow-up was limited.

Analyses denoting a recorded prescription of systemic antiviral treatment with acyclovir, valaciclovir or famciclovir within 28 days of the first vaccination prescription as event are shown in Tables 24 to 27, in patients with and without immunodeficiency. The number of events in this analysis is lower, but the pattern is similar as the approach of counting ICD Codes for herpes zoster as events and are therefore supporting the results of this analysis approach.

Outcomes recorded during 1-28 days after the second vaccination prescription are shown in Tables 28 to 31. No outcomes were recorded after the third vaccination prescription. Overall, the number of events are too small to allow for any meaningful interpretation of analyses relating to 2nd prescriptions of vaccines.

5. Discussion of results

5.1. Summary of results

Main results:

Inactivated varicella zoster vaccine vs. Live attenuated varicella zoster vaccine

Compared to live attenuated varicella zoster vaccine the frequency of zoster outcome events in patients that had received a prescription for inactivated varicella zoster vaccine was similar, but there was limited data on live attenuated varicella zoster vaccine in middle aged and older patients. Also, very few patients with immunosuppression had received live attenuated varicella zoster vaccine.

Inactivated varicella zoster vaccine vs. Pneumococcal vaccine

Overall, higher event rates of herpes zoster seem to be observed in patients receiving inactivated herpes zoster vaccines as compared to pneumococcal vaccines. However, due to differences in the treated populations, possible misclassification of outcome events and a limited total number of outcome events it cannot be confirmed whether inactivated herpes zoster vaccine is indeed associated with an increased risk of herpes zoster compared to pneumococcal vaccine.

Trends were similar but events were much fewer for treatment with acyclovir, valaciclovir or famciclovir between 1-28 days after the vaccination prescription in patients without a history of immunodeficiency. Treatment with acyclovir, valaciclovir or famciclovir in patients without a history of immunodeficiency circumvents limitations of possible miscoding of prior herpes zoster events as new events. In patients with a history of immunodeficiency a more similar proportion of patients received treatment with acyclovir, valaciclovir or famciclovir between 1-28 days after the vaccination prescription, which is consistent with the possibility that such patients may receive antiviral treatment prophylactically.

Differences between patients treated with different vaccines:

The proportion of patients with a history of immunodeficiency was, as expected, lower in patients with a prescription for live attenuated varicella zoster vaccine vs. patients with a prescription for inactivated varicella zoster vaccine or patients with a prescription for pneumococcal vaccine (3.7% vs. 8.8-8.9% and 7.0%). However, including also corticosteroids as immunosuppressive agents, results were more similar between the groups (12.0% vs. 12.7-13.5% and 15.7%). Patients with a prescription for inactivated varicella zoster vaccine had the oldest age distribution and patients with a prescription for live attenuated varicella zoster vaccine had the youngest age distribution. Patients with a prescription for inactivated varicella zoster vaccine had the lowest percentage of females and patients with a prescription for patients with a history of varicella zoster was highest among prescriptions for inactivated varicella zoster vaccine had the lowest percentage of females. The percentage of patients with a history of varicella zoster was highest among prescriptions for inactivated varicella zoster vaccine had the lowest percentage of females. The percentage of patients with a history of varicella zoster was highest among prescriptions for inactivated varicella zoster vaccine (25.9-27.2% vs. 5.3% (live attenuated varicella zoster vaccine) and 6.1% (pneumococcal vaccine)).

Possible risk groups for herpes zoster outcomes:

Zoster outcomes were more frequent in patients with a history of varicella or zoster than in patients without such a history suggesting that a history of varicella or zoster is a risk factor for a recurrent herpes zoster event. The fact that only a small number of patients had a history of immunodeficiency

made it difficult to compare the rate of herpes zoster in this group to patients with no history of immunodeficiency, although data are compatible with an expected higher frequency herpes zoster events in patients with a history of immunodeficiency.

No patient aged 2-17 years or 18 to 29 years had a zoster outcome recorded 1-28 days after the vaccination prescription. In the remaining age groups of patients 30 to 99 years there was no clear evidence of an increasing risk with increasing age, which could be due to a higher frequency of other risk factors besides age in younger vaccinated patients.

5.2. Strengths

The study evaluated a limited follow-up period after a vaccination prescription in patients with a minimum observation period prior to the vaccination prescription. Patients were required to be observable during the entire follow-up period as indicated by a consultation at the end of the follow-up period or later. Because the study period itself is recent, all consultations by the patient at the end of or after the follow-up period are also recent, which ensures that only patients actively consulting the physician practice during the entire study period are included in the study.

5.3. Limitations

Due to the free doctor's choice in Germany it is possible for patients to visit multiple physicians without the need for a referral. Therefore, it is possible that not all diagnoses and treatments are captured in IMS® Disease Analyzer Germany, where a patient can only be uniquely identified within the same practice. In the current study this risk has been minimised by selecting a short study period and including only patients actively consulting the physician practice during the entire study period.

Patients vaccinated with different types of vaccines are likely to have different underlying risk factors that may affect the risk of herpes zoster. It is also possible that physicians are more actively recording risk factors for herpes zoster such as a prior history of herpes zoster in patients that receive a varicella zoster vaccine compared to patients that receive a pneumococcal vaccine. A prior history of herpes zoster might be miscoded as a new occurrence of herpes zoster if it is not clearly recorded that the diagnostic certainty of the herpes zoster is 'condition after'. This might be particularly the case if the vaccination date occurs after the prescription date. Moreover, it cannot be excluded that patients and physicians are more observant of possible symptoms of herpes zoster following varicella zoster vaccination vs. pneumococcal vaccination and are therefore more likely to record such events in these patients.

In patients with immunodeficiency, depending on the severity of the condition, patients may require prophylactic antiviral treatment, which makes these patients particularly difficult to study.

This study is descriptive and provides only stratified analyses of occurrence of herpes zoster by age group, gender and type of vaccine. No regression analysis was applied to consider simultaneously the effect of multiple potential confounders. Moreover, only a fixed follow-up time of 28 or 56 days was considered.

5.4. Statistical power

Not applicable.

5.5. Risk of bias

• Selection of patient population: See section 5.3.

- $_{\odot}$ $\,$ Validity of measurement of exposure and outcome: See section 5.3.
- Unmeasured/uncontrolled confounding: See section 5.3.

5.6. External validity and Generalisability

The findings in this study are hypothesis generating and require confirmation. Similar studies in other databases would also be desirable.

5.7. Interpretation

The current study adds limited data to the question of whether vaccination with inactivated varicella zoster vaccine increases the risk of herpes zoster in comparison to pneumococcal vaccine, another inactivated vaccine. The study does show that patients with a prescription for inactivated varicella zoster vaccine were more likely to have risk factors for herpes zoster (e.g. older age, a higher frequency of females, a higher frequency of prior varicella or zoster) compared to patients with a prescription for pneumococcal vaccine. The number of events and the frequency of events observed seem to be higher in patients with inactivated varicella zoster vaccine compared to patients with pneumococcal vaccine, but are based on a very low number events and interpretation of subgroups is based on small populations not allowing any firm conclusions. A larger study would be needed to answer this question taking known risk factors for herpes zoster into account and focusing on a herpes zoster outcome with a minimal risk of misclassification. A better characterisation of the risk factors for herpes zoster might also be needed. In order to avoid misclassification, it is suggested to limit the outcome to herpes zoster events that require antiviral treatment in patients with no history of immunodeficiency. Considering an increasing number of patients with a prescription for inactivated varicella zoster vaccine over time, it might be worth repeating the study including data from all of 2019.

6. Other Information

Not applicable.

7. Conclusion

The question of whether vaccination with inactivated varicella zoster vaccine increases the risk of herpes zoster in comparison to pneumococcal vaccine, another inactivated vaccine, cannot be answered by this study.

8. References



9. Main tables

Table 1 Number and frequency of herpes zoster events 1-28 days after a vaccination prescription in patients receiving inactivated (IA) and live attenuated (LA) Varizella Zoster (VZ) vaccines, stratified by a history of

mmunodeficiency/immunosuppression (1D) and a history of VZ									
	Patients	without hi	istory of I	D	Patients with history of ID				
	No history of VZ		With history of VZ		No histo	y of VZ	With history of VZ		
	IA VZ vaccine	LA VZ vaccine	IA VZ vaccine	LA VZ vaccine	IA VZ vaccine	LA VZ vaccine	IA VZ vaccine	LA VZ vaccine	
Number of patients (age 2-99)	2010	1163	686	63	180	42	80	5	
Patients with outcome	11	0	37	2	2	0	6	0	
Outcome rate per 1000 patients (95% CI)	5.5 (3.1- 9.8)	0.0 (0.0- 3.3)	53.9 (39.4- 73.5)	31.7 (8.7- 108.6)	11.1 (3.1- 39.6)	0.0 (0.0- 104.4)	75.0 (34.8- 154.1)	0.0 (0.0- 434.5)	

CI = confidence interval.

Table 2 Number and frequency of herpes zoster events 1-28 days after a vaccination prescription in patients receiving inactivated (IA) Varizella Zoster (VZ) vaccine and pneumococcal vaccine, stratified by a history of immunodeficiency/immunosuppression and a history of VZ

	Patients without history of ID				Patients with history of ID			
	No history	of VZ	With history of VZ		No history of VZ		With history of VZ	
	IA VZ vaccine	Pneumo coccal vaccine	IA VZ vaccine	Pneumo coccal vaccine	IA VZ vaccine	Pneumo coccal vaccine	IA VZ vaccine	Pneumo coccal vaccine
Number of patients (age 2-99)	1825	4735	667	291	164	335	78	41
Patients with outcome	10	4	37	1	1	0	6	0
Outcome rate per 1000 patients (95% CI)	5.5 (3.0- 10.1)	0.8 (0.3-2.2)	55.5 (40.5- 75.5)	3.4 (0.6-19.2	6.1 (1.1- 33.7)	0.0 (0.0- 11.3)	76.9 (35.7- 157.8)	0.0 (0.0- 85.7)

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CI = confidence interval.

Table 3 Distribution of patients by included age groups, vaccination type andhistory of immunodeficiency/immunosuppression (ID/IS)

		All ages*	Ages 2-99 years
IA vs. LA VZ vaccine	IA VZ	3000	2956 (98.5%)
	LA VZ	3023	1273 (42.1%)
IA vs. pneumococcal vaccine	IA VZ	2740	2734 (99.8%)
	All pneumococcal	7428	5402 (72.7%)
	Conjugated pneumococcal	3933	2200 (55.9%)
	Unconjugated pneumococcal	3495	3202 (91.6%)

IA = inactivated, LA = live attenuated, VZ =varicella zoster.

* Includes patients 0-1 years and patients with unknown age (including patients over 99 years).

Table 4 Patients without a history of immunodeficiency/immunosuppression: Included patients with a prescription for inactivated varicella zoster (VZ) or live attenuated VZ vaccine and recorded outcomes

	Inact	ivated VZ vac	cine	Live attenuated VZ vaccine			
	All patients	Patients with outcome	Per 1000 patients	All patients	Patients with outcome	Per 1000 patients	
Total	2696	48	17.8	1226	2	1.6	
Females	1532	30	19.6	639	1	1.6	
Males	1150	18	15.7	577	1	1.7	
2-17 years	15	0	0.0	809	0	0.0	
18-29 years	27	0	0.0	155	0	0.0	
30-49 years	62	4	64.5	101	1	9.9	
50-59 years	289	5	17.3	31	1	32.3	
60-69 years	899	17	18.9	55	0	0.0	
70-79 years	981	14	14.3	47	0	0.0	
80-89 years	392	5	12.8	27	0	0.0	
90-99 years	31	3	96.8	1	0	0.0	
Hx VZ	686	37	53.9	63	2	31.7	
Hx Z	677	36	53.2	39	2	51.3	
No hx VZ	2010	11	5.5	1163	0	0.0	

Table 5 Patients with a history of immunodeficiency/immunosuppression:Included patients with a prescription for inactivated varicella zoster (VZ) or liveattenuated VZ vaccine and recorded outcomes

	Inact	ivated VZ vacci	ne	Live attenuate	d VZ vaccine	
	All patients	Patients with outcome	Per 1000 patients	All patients	Patients with outcome	Per 1000 patients
Total	260	8	30.8	47	0	0.0
Females	149	2	13.4	26	0	0.0
Males	110	6	54.5	21	0	0.0
2-17 years	0			24	0	0.0
18-29 years	2	0	0.0	8	0	0.0
30-49 years	7	0	0.0	6	0	0.0
50-59 years	32	0	0.0	2	0	0.0
60-69 years	91	3	33.0	3	0	0.0
70-79 years	83	4	48.2	3	0	0.0
80-89 years	42	0	0.0	1	0	0.0
90-99 years	3	1	333.3	0		
Hx VZ	80	6	75.0	5	0	0.0
Hx Z	78	6	76.9	5	0	0.0
No hx VZ	180	2	11.1	42	0	0.0

Table 6 Patients without a history of immunodeficiency/immunosuppression: Included patients with a prescription for inactivated varicella zoster (VZ) or pneumococcal vaccine and recorded outcomes

	Inactiv	vated VZ vacci	ne	Pneumococcal vaccine			
	All patients	Patients with outcome	Per 1000 patients	All patients	Patients with outcome	Per 1000 patients	
Total	2492	47	18.9	5026	5	1.0	
Females	1452	30	20.7	2239	4	1.8	
Males	1040	17	16.3	2744	1	0.4	
2-17 years	0			870	0	0.0	
18-29 years	5	0	0.0	214	0	0.0	
30-49 years	56	4	71.4	180	0	0.0	
50-59 years	278	5	18.0	349	0	0.0	
60-69 years	834	16	19.2	1470	1	0.7	
70-79 years	914	14	15.3	1352	3	2.2	
80-89 years	375	5	13.3	534	1	1.9	
90-99 years	30	3	100.0	57	0	0.0	
Hx VZ	667	37	55.5	291	1	3.4	
Hx Z	659	36	54.6	254	1	3.6	
No hx VZ	1825	10	5.5	4735	4	0.8	

Table 7 Patients with a history of immunodeficiency/immunosuppression: Includedpatients with a prescription for inactivated varicella zoster (VZ) or pneumococcalvaccine and recorded outcomes

	Inact	ivated VZ vacci	ne	Pneumococcal vaccine			
	All patients	Patients with outcome	Per 1000 patients	All patients	Patients with outcome	Per 1000 patients	
Total	242	7	28.9	376	0	0.0	
Females	142	2	14.1	196	0	0.0	
Males	100	5	50.0	179	0	0.0	
2-17 years	0			51	0	0.0	
18-29 years	1	0	0.0	15	0	0.0	
30-49 years	6	0	0.0	30	0	0.0	
50-59 years	29	0	0.0	56	0	0.0	
60-69 years	84	3	35.7	89	0	0.0	
70-79 years	79	3	38.0	95	0	0.0	
80-89 years	40	0	0.0	36	0	0.0	
90-99 years	3	1	333.3	4	0	0.0	
Hx VZ	78	6	76.9	41	0	0.0	
Hx Z	76	6	78.9	40	0	0.0	
No hx VZ	164	1	6.1	335	0	0.0	



Table 8 Patients without a history of immunodeficiency/immunosuppression: Included patients with a prescription for inactivated varicella zoster (VZ) or pneumococcal vaccine and recorded outcomes by pneumococcal vaccine subtype

	Inactivated VZ vaccine		Conjugated pneumococcal vaccine			Unconjugated pneumococcal vaccine			
	All patients	Patients with outcome	Per 1000 patients	All patients	Patients with outcome	Per 1000 patients	All patients	Patients with outcome	Per 1000 patients
Total	2492	47	18.9	2025	4	2.0	3001	1	0.3
Females	1452	30	20.7	934	3	3.2	1305	1	0.8
Males	1040	17	16.3	1073	1	0.9	1671	0	0.0
2-17 years	0			707	0	0.0	163	0	0.0
18-29 years	5	0	0.0	88	0	0.0	126	0	0.0
30-49 years	56	4	71.4	93	0	0.0	87	0	0.0
50-59 years	278	5	18.0	156	0	0.0	193	0	0.0
60-69 years	834	16	19.2	426	1	2.3	1044	0	0.0
70-79 years	914	14	15.3	398	2	5.0	954	1	1.0
80-89 years	375	5	13.3	144	1	6.9	390	0	0.0
90-99 years	30	3	100.0	13	0	0.0	44	0	0.0
Hx VZ	667	37	55.5	95	1	10.5	196	0	0.0
Hx Z	659	36	54.6	84	1	11.9	190	0	0.0
No hx VZ	1825	10	5.5	1930	3	1.6	2805	1	0.4

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Table 9 Patients without a history of immunodeficiency/immunosuppression (incl. corticosteroids): Included patients with a prescription for inactivated varicella zoster (VZ) or pneumococcal vaccine and recorded outcomes by pneumococcal vaccine subtype

	Inactivated VZ vaccine		Conjugated pneumococcal vaccine			Unconjugated pneumococcal vaccine			
	All patients	Patients with outcome	Per 1000 patients	All patients	Patients with outcome	Per 1000 patients	All patients	Patients with outcome	Per 1000 patients
Total	2387	44	18.4	1803	4	2.2	2751	1	0.4
Females	1383	27	19.5	839	3	3.6	1207	1	0.8
Males	1004	17	16.9	955	1	1.0	1536	0	0.0
2-17 years	0			648	0	0.0	113	0	0.0
18-29 years	3	0	0.0	52	0	0.0	79	0	0.0
30-49 years	49	4	81.6	82	0	0.0	77	0	0.0
50-59 years	259	5	19.3	120	0	0.0	171	0	0.0
60-69 years	811	16	19.7	400	1	2.5	1000	0	0.0
70-79 years	878	12	13.7	358	2	5.6	901	1	1.1
80-89 years	361	4	11.1	132	1	7.6	369	0	0.0
90-99 years	26	3	115.4	11	0	0.0	41	0	0.0
Hx VZ	633	34	53.7	83	1	12.0	181	0	0.0
Hx Z	625	33	52.8	74	1	13.5	175	0	0.0
No hx VZ	1754	10	5.7	1720	3	1.7	2570	1	0.4



Table 10 Patients without a history of immunodeficiency/immunosuppression:Included patients with a prescription for inactivated varicella zoster (VZ) or liveattenuated VZ vaccine and recorded outcomes after the vaccination date

	Inactivated VZ vaccine			Live attenuated VZ vaccine			
	All patients	Patients with outcome	Per 1000 patients	All patients	Patients with outcome	Per 1000 patients	
Total	2696	38	14.1	1226	2	1.6	
Females	1532	23	15.0	639	1	1.6	
Males	1150	15	13.0	577	1	1.7	
2-17 years	15	0	0.0	809	0	0.0	
18-29 years	27	0	0.0	155	0	0.0	
30-49 years	62	4	64.5	101	1	9.9	
50-59 years	289	4	13.8	31	1	32.3	
60-69 years	899	10	11.1	55	0	0.0	
70-79 years	981	12	12.2	47	0	0.0	
80-89 years	392	5	12.8	27	0	0.0	
90-99 years	31	3	96.8	1	0	0.0	
Hx VZ	686	28	40.8	63	2	31.7	
Hx Z	677	28	41.4	39	2	51.3	
No hx VZ	2010	10	5.0	1163	0	0.0	

Hx = history of, VZ = varicella zoster, Z = zoster.

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Table 11 Patients with a history of immunodeficiency/immunosuppression:Included patients with a prescription for inactivated varicella zoster (VZ) or liveattenuated VZ vaccine and recorded outcomes after the vaccination date

	Inact	ivated VZ vacci	ne	Live attenuated VZ vaccine			
	All patients	Patients with outcome	Per 1000 patients	All patients	Patients with outcome	Per 1000 patients	
Total	260	6	23.1	47	0	0.0	
Females	149	1	6.7	26	0	0.0	
Males	110	5	45.5	21	0	0.0	
2-17 years	0			24	0	0.0	
18-29 years	2	0	0.0	8	0	0.0	
30-49 years	7	0	0.0	6	0	0.0	
50-59 years	32	0	0.0	2	0	0.0	
60-69 years	91	3	33.0	3	0	0.0	
70-79 years	83	2	24.1	3	0	0.0	
80-89 years	42	0	0.0	1	0	0.0	
90-99 years	3	1	333.3	0			
Hx VZ	80	4	50.0	5	0	0.0	
Hx Z	78	4	51.3	5	0	0.0	
No hx VZ	180	2	11.1	42	0	0.0	

Table 12 Patients without a history of immunodeficiency/immunosuppression:Included patients with a prescription for inactivated varicella zoster (VZ) orpneumococcal vaccine and recorded outcomes after the vaccination date

	Inactiv	Inactivated VZ vaccine			Pneumococcal vaccine			
	All patients	Patients with outcome	Per 1000 patients	All patients	Patients with outcome	Per 1000 patients		
Total	2492	37	14.8	5026	5	1.0		
Females	1452	23	15.8	2239	4	1.8		
Males	1040	14	13.5	2744	1	0.4		
2-17 years	0			870	0	0.0		
18-29 years	5	0	0.0	214	0	0.0		
30-49 years	56	4	71.4	180	0	0.0		
50-59 years	278	4	14.4	349	0	0.0		
60-69 years	834	9	10.8	1470	1	0.7		
70-79 years	914	12	13.1	1352	3	2.2		
80-89 years	375	5	13.3	534	1	1.9		
90-99 years	30	3	100.0	57	0	0.0		
Hx VZ	667	28	42.0	291	1	3.4		
Hx Z	659	28	42.5	254	1	3.6		
No hx VZ	1825	9	4.9	4735	4	0.8		

Table 13 Patients with a history of immunodeficiency/immunosuppression:Included patients with a prescription for inactivated varicella zoster (VZ) orpneumococcal vaccine and recorded outcomes after the vaccination date

	Inact	ivated VZ vacci	ne	Pneumococcal vaccine		
	All patients	Patients with outcome	Per 1000 patients	All patients	Patients with outcome	Per 1000 patients
Total	242	5	20.7	376	0	0.0
Females	142	1	7.0	196	0	0.0
Males	100	4	40.0	179	0	0.0
2-17 years	0			51	0	0.0
18-29 years	1	0	0.0	15	0	0.0
30-49 years	6	0	0.0	30	0	0.0
50-59 years	29	0	0.0	56	0	0.0
60-69 years	84	3	35.7	89	0	0.0
70-79 years	79	1	12.7	95	0	0.0
80-89 years	40	0	0.0	36	0	0.0
90-99 years	3	1	333.3	4	0	0.0
Hx VZ	78	4	51.3	41	0	0.0
Hx Z	76	4	52.6	40	0	0.0
No hx VZ	164	1	6.1	335	0	0.0

Table 14 Patients without a history of immunodeficiency/immunosuppression: Included patients with a prescription for inactivated varicella zoster (VZ) or live attenuated VZ vaccine and recorded outcomes with a diagnosis certainty of 'confirmed'

	Inact	ivated VZ vac	cine	Live attenuated VZ vaccine			
	All patients	Patients with outcome	Per 1000 patients	All patients	Patients with outcome	Per 1000 patients	
Total	2696	46	17.1	1226	2	1.6	
Females	1532	29	18.9	639	1	1.6	
Males	1150	17	14.8	577	1	1.7	
2-17 years	15	0	0.0	809	0	0.0	
18-29 years	27	0	0.0	155	0	0.0	
30-49 years	62	4	64.5	101	1	9.9	
50-59 years	289	5	17.3	31	1	32.3	
60-69 years	899	15	16.7	55	0	0.0	
70-79 years	981	14	14.3	47	0	0.0	
80-89 years	392	5	12.8	27	0	0.0	
90-99 years	31	3	96.8	1	0	0.0	
Hx VZ	686	36	52.5	63	2	31.7	
Hx Z	677	35	51.7	39	2	51.3	
No hx VZ	2010	10	5.0	1163	0	0.0	

Table 15 Patients without a history of immunodeficiency/immunosuppression: Included patients with a prescription for inactivated varicella zoster (VZ) or pneumococcal vaccine and recorded outcomes with a diagnosis certainty of 'confirmed'

	Inactivated VZ vaccine			Pneumococcal vaccine			
	All patients	Patients with outcome	Per 1000 patients	All patients	Patients with outcome	Per 1000 patients	
Total	2492	45	18.1	5026	5	1.0	
Females	1452	29	20.0	2239	4	1.8	
Males	1040	16	15.4	2744	1	0.4	
2-17 years	0			870	0	0.0	
18-29 years	5	0	0.0	214	0	0.0	
30-49 years	56	4	71.4	180	0	0.0	
50-59 years	278	5	18.0	349	0	0.0	
60-69 years	834	14	16.8	1470	1	0.7	
70-79 years	914	14	15.3	1352	3	2.2	
80-89 years	375	5	13.3	534	1	1.9	
90-99 years	30	3	100.0	57	0	0.0	
Hx VZ	667	36	54.0	291	1	3.4	
Hx Z	659	35	53.1	254	1	3.6	
No hx VZ	1825	9	4.9	4735	4	0.8	

Table 16 Patients without a history of immunodeficiency/immunosuppression: Included patients with a prescription for inactivated varicella zoster (VZ) or live attenuated VZ vaccine and recorded outcomes excluding post zoster neuralgia and medical event texts suggesting prophylaxis

	Inactiv	vated VZ vac	cine	Live attenuated VZ vaccine			
	All patients	Patients with outcome	Per 1000 patients	All patients	Patients with outcome	Per 1000 patients	
Total	2696	34	12.6	1226	2	1.6	
Females	1532	25	16.3	639	1	1.6	
Males	1150	9	7.8	577	1	1.7	
2-17 years	15	0	0.0	809	0	0.0	
18-29 years	27	0	0.0	155	0	0.0	
30-49 years	62	4	64.5	101	1	9.9	
50-59 years	289	4	13.8	31	1	32.3	
60-69 years	899	11	12.2	55	0	0.0	
70-79 years	981	11	11.2	47	0	0.0	
80-89 years	392	3	7.7	27	0	0.0	
90-99 years	31	1	32.3	1	0	0.0	
Hx VZ	686	27	39.4	63	2	31.7	
Hx Z	677	27	39.9	39	2	51.3	
No hx VZ	2010	7	3.5	1163	0	0.0	

Table 17 Patients with a history of immunodeficiency/immunosuppression: Included patients with a prescription for inactivated varicella zoster (VZ) or live attenuated VZ vaccine and recorded outcomes excluding post zoster neuralgia and medical event texts suggesting prophylaxis

	Inactiv	vated VZ vac	cine	Live attenuated VZ vaccine			
	All patients	Patients with outcome	Per 1000 patients	All patients	Patients with outcome	Per 1000 patients	
Total	260	4	15.4	47	0	0.0	
Females	149	2	13.4	26	0	0.0	
Males	110	2	18.2	21	0	0.0	
2-17 years	0			24	0	0.0	
18-29 years	2	0	0.0	8	0	0.0	
30-49 years	7	0	0.0	6	0	0.0	
50-59 years	32	0	0.0	2	0	0.0	
60-69 years	91	2	22.0	3	0	0.0	
70-79 years	83	1	12.0	3	0	0.0	
80-89 years	42	0	0.0	1	0	0.0	
90-99 years	3	1	333.3	0			
Hx VZ	80	3	37.5	5	0	0.0	
Hx Z	78	3	38.5	5	0	0.0	
No hx VZ	180	1	5.6	42	0	0.0	

Table 18 Patients without a history of immunodeficiency/immunosuppression: Included patients with a prescription for inactivated varicella zoster (VZ) or pneumococcal vaccine and recorded outcomes excluding post zoster neuralgia and medical event texts suggesting prophylaxis

	Inactiv	vated VZ vac	cine	Pneumococcal vaccine			
	All patients	Patients with outcome	Per 1000 patients	All patients	Patients with outcome	Per 1000 patients	
Total	2492	34	13.6	5026	4	0.8	
Females	1452	25	17.2	2239	3	1.3	
Males	1040	9	8.7	2744	1	0.4	
2-17 years	0			870	0	0.0	
18-29 years	5	0	0.0	214	0	0.0	
30-49 years	56	4	71.4	180	0	0.0	
50-59 years	278	4	14.4	349	0	0.0	
60-69 years	834	11	13.2	1470	1	0.7	
70-79 years	914	11	12.0	1352	2	1.5	
80-89 years	375	3	8.0	534	1	1.9	
90-99 years	30	1	33.3	57	0	0.0	
Hx VZ	667	27	40.5	291	1	3.4	
Hx Z	659	27	41.0	254	1	3.6	
No hx VZ	1825	7	3.8	4735	3	0.6	

Table 19 Patients with a history of immunodeficiency/immunosuppression: Included patients with a prescription for inactivated varicella zoster (VZ) or pneumococcal vaccine and recorded outcomes excluding post zoster neuralgia and medical event texts suggesting prophylaxis

	Inactiv	vated VZ vac	cine	Pneumococcal vaccine			
	All patients	Patients with outcome	Per 1000 patients	All patients	Patients with outcome	Per 1000 patients	
Total	242	4	16.5	376	0	0.0	
Females	142	2	14.1	196	0	0.0	
Males	100	2	20.0	179	0	0.0	
2-17 years	0			51	0	0.0	
18-29 years	1	0	0.0	15	0	0.0	
30-49 years	6	0	0.0	30	0	0.0	
50-59 years	29	0	0.0	56	0	0.0	
60-69 years	84	2	23.8	89	0	0.0	
70-79 years	79	1	12.7	95	0	0.0	
80-89 years	40	0	0.0	36	0	0.0	
90-99 years	3	1	333.3	4	0	0.0	
Hx VZ	78	3	38.5	41	0	0.0	
Hx Z	76	3	39.5	40	0	0.0	
No hx VZ	164	1	6.1	335	0	0.0	

Table 20 Patients without a history of immunodeficiency/immunosuppression:Included patients with a prescription for inactivated varicella zoster (VZ) or liveattenuated VZ vaccine and recorded outcomes during an extended follow-up periodof 56 days

	Inactiv	vated VZ vac	cine	Live attenuated VZ vaccine			
	All patients	Patients with outcome	Per 1000 patients	All patients	Patients with outcome	Per 1000 patients	
Total	1822	60	32.9	1057	2	1.9	
Females	1050	42	40.0	551	1	1.8	
Males	771	18	23.3	497	1	2.0	
2-17 years	3	0	0.0	692	0	0.0	
18-29 years	6	0	0.0	135	0	0.0	
30-49 years	47	4	85.1	91	1	11.0	
50-59 years	227	7	30.8	30	1	33.3	
60-69 years	612	18	29.4	47	0	0.0	
70-79 years	652	16	24.5	39	0	0.0	
80-89 years	255	11	43.1	22	0	0.0	
90-99 years	20	4	200.0	1	0	0.0	
Hx VZ	482	49	101.7	56	2	35.7	
Hx Z	475	49	103.2	37	2	54.1	
No hx VZ	1340	11	8.2	1001	0	0.0	

Table 21 Patients with a history of immunodeficiency/immunosuppression: Included patients with a prescription for inactivated varicella zoster (VZ) or live attenuated VZ vaccine and recorded outcomes during an extended follow-up period of 56 days

	Inactiv	vated VZ vac	cine	Live attenuated VZ vaccine			
	All patients	Patients with outcome	Per 1000 patients	All patients	Patients with outcome	Per 1000 patients	
Total	194	9	46.4	43	0	0.0	
Females	111	5	45.0	22	0	0.0	
Males	83	4	48.2	21	0	0.0	
2-17 years	0			23	0	0.0	
18-29 years	1	0	0.0	7	0	0.0	
30-49 years	6	0	0.0	4	0	0.0	
50-59 years	29	0	0.0	2	0	0.0	
60-69 years	68	2	29.4	3	0	0.0	
70-79 years	61	3	49.2	3	0	0.0	
80-89 years	27	3	111.1	1	0	0.0	
90-99 years	2	1	500.0	0	0	0.0	
Hx VZ	62	8	129.0	5	0	0.0	
Hx Z	60	8	133.3	4	0	0.0	
No hx VZ	132	1	7.6	38	0	0.0	

Table 22 Patients without a history of immunodeficiency/immunosuppression: Included patients with a prescription for inactivated varicella zoster (VZ) or pneumococcal vaccine and recorded outcomes during an extended follow-up period of 56 days

	Inactivated VZ vaccine			Pneumococcal vaccine			
	All patients	Patients with outcome	Per 1000 patients	All patients	Patients with outcome	Per 1000 patients	
Total	1721	60	34.9	4669	7	1.5	
Females	1011	43	42.5	2080	4	1.9	
Males	710	17	23.9	2546	3	1.2	
2-17 years	0	0		795	0	0.0	
18-29 years	3	0	0.0	204	0	0.0	
30-49 years	46	4	87.0	175	0	0.0	
50-59 years	220	7	31.8	319	1	3.1	
60-69 years	574	18	31.4	1360	2	1.5	
70-79 years	611	16	26.2	1267	3	2.4	
80-89 years	248	11	44.4	496	1	2.0	
90-99 years	19	4	210.5	53	0	0.0	
Hx VZ	473	50	105.7	273	2	7.3	
Hx Z	467	50	107.1	259	2	7.7	
No hx VZ	1248	10	8.0	4396	5	1.1	

Table 23 Patients with a history of immunodeficiency/immunosuppression: Included patients with a prescription for inactivated varicella zoster (VZ) or pneumococcal vaccine and recorded outcomes during an extended follow-up period of 56 days

	Inactivated VZ vaccine			Pneumococcal vaccine			
	All patients	Patients with outcome	Per 1000 patients	All patients	Patients with outcome	Per 1000 patients	
Total	181	9	49.7	356	0	0.0	
Females	106	5	47.2	186	0	0.0	
Males	75	4	53.3	169	0	0.0	
2-17 years	0	0		48	0	0.0	
18-29 years	1	0	0.0	14	0	0.0	
30-49 years	5	0	0.0	28	0	0.0	
50-59 years	26	0	0.0	55	0	0.0	
60-69 years	62	2	32.3	78	0	0.0	
70-79 years	59	3	50.8	94	0	0.0	
80-89 years	26	3	115.4	35	0	0.0	
90-99 years	2	1	500.0	4	0	0.0	
Hx VZ	60	8	133.3	40	0	0.0	
Hx Z	58	8	137.9	39	0	0.0	
No hx VZ	121	1	8.3	316	0	0.0	

Table 24 Patients without a history of immunodeficiency/immunosuppression: Included patients with a prescription for inactivated varicella zoster (VZ) or live attenuated VZ vaccine and treatment with acyclovir, valaciclovir or famciclovir during 1-28 days after the vaccination prescription

	Inactivated VZ vaccine			Live attenuated VZ vaccine			
	All patients	Patients with outcome	Per 1000 patients	All patients	Patients with outcome	Per 1000 patients	
Total	2696	9	3.3	1226	0	0.0	
Females	1532	8	5.2	639	0	0.0	
Males	1150	1	0.9	577	0	0.0	
2-17 years	15	0	0.0	809	0	0.0	
18-29 years	27	0	0.0	155	0	0.0	
30-49 years	62	0	0.0	101	0	0.0	
50-59 years	289	3	10.4	31	0	0.0	
60-69 years	899	1	1.1	55	0	0.0	
70-79 years	981	1	1.0	47	0	0.0	
80-89 years	392	3	7.7	27	0	0.0	
90-99 years	31	1	32.3	1	0	0.0	
Hx VZ	686	7	10.2	63	0	0.0	
Hx Z	677	7	10.3	39	0	0.0	
No hx VZ	2010	2	1.0	1163	0	0.0	

Table 25 Patients with a history of immunodeficiency/immunosuppression: Included patients with a prescription for inactivated varicella zoster (VZ) or live attenuated VZ vaccine and treatment with acyclovir, valaciclovir or famciclovir during 1-28 days after the vaccination prescription

	Inactiv	vated VZ vac	cine	Live attenuated VZ vaccine			
	All patients	Patients with outcome	Per 1000 patients	All patients	Patients with outcome	Per 1000 patients	
Total	260	6	23.1	47	0	0.0	
Females	149	3	20.1	26	0	0.0	
Males	110	3	27.3	21	0	0.0	
2-17 years	0			24	0	0.0	
18-29 years	2	0	0.0	8	0	0.0	
30-49 years	7	1	142.9	6	0	0.0	
50-59 years	32	1	31.3	2	0	0.0	
60-69 years	91	3	33.0	3	0	0.0	
70-79 years	83	0	0.0	3	0	0.0	
80-89 years	42	1	23.8	1	0	0.0	
90-99 years	3	0	0.0	0			
Hx VZ	80	3	37.5	5	0	0.0	
Hx Z	78	3	38.5	5	0	0.0	
No hx VZ	180	3	16.7	42	0	0.0	

Table 26 Patients without a history of immunodeficiency/immunosuppression: Included patients with a prescription for inactivated varicella zoster (VZ) or pneumococcal vaccine and treatment with acyclovir, valaciclovir or famciclovir during 1-28 days after the vaccination prescription

	Inactivated VZ vaccine			Pneumococcal vaccine			
	All patients	Patients with outcome	Per 1000 patients	All patients	Patients with outcome	Per 1000 patients	
Total	1721	8	4.6	4669	2	0.4	
Females	1011	8	7.9	2080	2	1.0	
Males	710	0	0.0	2546	0	0.0	
2-17 years	0			795	0	0.0	
18-29 years	3	0	0.0	204	0	0.0	
30-49 years	46	0	0.0	175	0	0.0	
50-59 years	220	3	13.6	319	0	0.0	
60-69 years	574	0	0.0	1360	1	0.7	
70-79 years	611	1	1.6	1267	1	0.8	
80-89 years	248	3	12.1	496	0	0.0	
90-99 years	19	1	52.6	53	0	0.0	
Hx VZ	473	7	14.8	273	0	0.0	
Hx Z	467	7	15.0	259	0	0.0	
No hx VZ	1248	1	0.8	4396	2	0.5	

Table 27 Patients with a history of immunodeficiency/immunosuppression: Included patients with a prescription for inactivated varicella zoster (VZ) or pneumococcal vaccine and treatment with acyclovir, valaciclovir or famciclovir during 1-28 days after the vaccination prescription

	Inactivated VZ vaccine			Pneumococcal vaccine			
	All patients	Patients with outcome	Per 1000 patients	All patients	Patients with outcome	Per 1000 patients	
Total	242	4	28.9	376	3	0.0	
Females	142	3	14.1	196	2	0.0	
Males	100	1	50.0	179	1	0.0	
2-17 years	0			51	0	0.0	
18-29 years	1	0	0.0	15	0	0.0	
30-49 years	6	1	0.0	30	1	0.0	
50-59 years	29	0	0.0	56	1	0.0	
60-69 years	84	2	35.7	89	1	0.0	
70-79 years	79	0	38.0	95	0	0.0	
80-89 years	40	1	0.0	36	0	0.0	
90-99 years	3	0	333.3	4	0	0.0	
Hx VZ	78	3	76.9	41	0	0.0	
Hx Z	76	3	78.9	40	0	0.0	
No hx VZ	164	1	6.1	335	3	0.0	

Table 28 Patients without a history of immunodeficiency/immunosuppression: Included patients with a 2nd prescription for inactivated varicella zoster (VZ) or live attenuated VZ vaccine and recorded outcomes

	Inact	ivated VZ vac	cine	Live attenuated VZ vaccine		
	All patients	Patients with outcome	Per 1000 patients	All patients	Patients with outcome	Per 1000 patients
Total	528	8	15.2	330	0	0.0
Females	296	5	16.9	148	0	0.0
Males	230	3	13.0	178	0	0.0
2-17 years	5	0	0.0	232	0	0.0
18-29 years	4	0	0.0	59	0	0.0
30-49 years	14	0	0.0	19	0	0.0
50-59 years	64	1	15.6	5	0	0.0
60-69 years	161	4	24.8	5	0	0.0
70-79 years	190	1	5.3	5	0	0.0
80-89 years	82	2	24.4	5	0	0.0
90-99 years	8	0	0.0	0		
Hx VZ	157	7	44.6	13	0	0.0
Hx Z	156	7	44.9	2	0	0.0
No hx VZ	371	1	2.7	317	0	0.0

Table 29 Patients without a history of immunodeficiency/immunosuppression: Included patients with a 2nd prescription for inactivated varicella zoster (VZ) or pneumococcal vaccine and recorded outcomes

	Inact	ivated VZ vac	cine	Pneumococcal vaccine			
	All patients	Patients with outcome	Per 1000 patients	All patients	Patients with outcome	Per 1000 patients	
Total	488	8	16.4	536	0	0.0	
Females	278	5	18.0	211	0	0.0	
Males	210	3	14.3	292	0	0.0	
2-17 years	0			185	0	0.0	
18-29 years	3	0	0.0	134	0	0.0	
30-49 years	11	0	0.0	29	0	0.0	
50-59 years	62	1	16.1	38	0	0.0	
60-69 years	145	4	27.6	67	0	0.0	
70-79 years	180	1	5.6	60	0	0.0	
80-89 years	79	2	25.3	21	0	0.0	
90-99 years	8	0	0.0	2			
Hx VZ	155	7	45.2	25	0	0.0	
Hx Z	154	7	45.5	17	0	0.0	
No hx VZ	333	1	3.0	511	0	0.0	

Table 30 Patients with a history of immunodeficiency/immunosuppression:Included patients with a 2nd prescription for inactivated varicella zoster (VZ) orlive attenuated VZ vaccine and recorded outcomes

	Inact	ivated VZ vac	cine	Live attenuated VZ vaccine		
	All patients	Patients with outcome	Per 1000 patients	All patients	Patients with outcome	Per 1000 patients
Total	36	1	27.8	10	0	0.0
Females	21	1	47.6	3	0	0.0
Males	15	0	0.0	7	0	0.0
2-17 years	0			5	0	0.0
18-29 years	1	0	0.0	3	0	0.0
30-49 years	1	0	0.0	1	0	0.0
50-59 years	2	0	0.0	0		
60-69 years	10	0	0.0	1	0	0.0
70-79 years	16	0	0.0	0		
80-89 years	4	1	250.0	0		
90-99 years	2	0	0.0	0		
Hx VZ	15	1	66.7	0		
Hx Z	15	1	66.7	0		
No hx VZ	21	0	0.0	10	0	0.0

Table 31 Patients with a history of immunodeficiency/immunosuppression:Included patients with a 2nd prescription for inactivated varicella zoster (VZ) orpneumococcal vaccine and recorded outcomes

	Inact	ivated VZ vac	cine	Pneumococcal vaccine		
	All patients	Patients with outcome	Per 1000 patients	All patients	Patients with outcome	Per 1000 patients
Total	36	1	27.8	29	0	0.0
Females	21	1	47.6	15	0	0.0
Males	15	0	0.0	13	0	0.0
2-17 years	0			5	0	0.0
18-29 years	1	0	0.0	7	0	0.0
30-49 years	1	0	0.0	3	0	0.0
50-59 years	2	0	0.0	2	0	0.0
60-69 years	10	0	0.0	6	0	0.0
70-79 years	16	0	0.0	4	0	0.0
80-89 years	4	1	250.0	1	0	0.0
90-99 years	2	0	0.0	1	0	0.0
Hx VZ	16	1	62.5	2	0	0.0
Hx Z	16	1	62.5	2	0	0.0
No hx VZ	20	0	0.0	27	0	0.0

10. Supplementary tables

Table S 1 Patients without a history of immunodeficiency/immunosuppression(incl. corticosteroids): Included patients with a prescription for inactivatedvaricella zoster (VZ) or live attenuated VZ vaccine and recorded outcomes

	Inactivated VZ vaccine			Live attenuated VZ vaccine			
	All patients	Patients with outcome	Per 1000 patients	All patients	Patients with outcome	Per 1000 patients	
Total	2557	45	17.6	1120	2	1.8	
Females	1449	27	18.6	602	1	1.7	
Males	1103	18	16.3	513	1	1.9	
2-17 years	6	0	0.0	757	0	0.0	
18-29 years	11	0	0.0	124	0	0.0	
30-49 years	52	4	76.9	94	1	10.6	
50-59 years	269	5	18.6	27	1	37.0	
60-69 years	873	17	19.5	51	0	0.0	
70-79 years	942	12	12.7	45	0	0.0	
80-89 years	377	4	10.6	22	0	0.0	
90-99 years	27	3	111.1	0			
Hx VZ	650	34	52.3	57	2	35.1	
Hx Z	641	33	51.5	36	2	55.6	
No hx VZ	1907	11	5.8	1063	0	0.0	

Table S 2 Patients with a history of immunodeficiency/immunosuppression (incl.corticosteroids): Included patients with a prescription for inactivated varicellazoster (VZ) or live attenuated VZ vaccine and recorded outcomes

	Inact	nactivated VZ vaccine		Live attenuated VZ vaccine		
	All patients	Patients with outcome	Per 1000 patients	All patients	Patients with outcome	Per 1000 patients
Total	399	11	27.6	153	0	0.0
Females	232	5	21.6	63	0	0.0
Males	157	6	38.2	85	0	0.0
2-17 years	9	0	0.0	76	0	0.0
18-29 years	18	0	0.0	39	0	0.0
30-49 years	17	0	0.0	13	0	0.0
50-59 years	52	0	0.0	6	0	0.0
60-69 years	117	3	25.6	7	0	0.0
70-79 years	122	6	49.2	5	0	0.0
80-89 years	57	1	17.5	6	0	0.0
90-99 years	7	1	142.9	1	0	0.0
Hx VZ	116	9	77.6	11	0	0.0
Hx Z	114	9	78.9	7	0	0.0
No hx VZ	283	2	7.1	142	0	0.0

Table S 3 Patients without a history of immunodeficiency/immunosuppression (incl. corticosteroids): Included patients with a prescription for inactivated varicella zoster (VZ) or pneumococcal vaccine and recorded outcomes

	Inactiv	vated VZ vacci	ne	Pneumococcal vaccine		
	All patients	Patients with outcome	Per 1000 patients	All patients	Patients with outcome	Per 1000 patients
Total	2387	44	18.4	4554	5	1.1
Females	1383	27	19.5	2046	4	2.0
Males	1004	17	16.9	2491	1	0.4
2-17 years	0			761	0	0.0
18-29 years	3	0	0.0	131	0	0.0
30-49 years	49	4	81.6	159	0	0.0
50-59 years	259	5	19.3	291	0	0.0
60-69 years	811	16	19.7	1400	1	0.7
70-79 years	878	12	13.7	1259	3	2.4
80-89 years	361	4	11.1	501	1	2.0
90-99 years	26	3	115.4	52	0	0.0
Hx VZ	633	34	53.7	264	1	3.8
Hx Z	625	33	52.8	249	1	4.0
No hx VZ	1754	10	5.7	4290	4	0.9

Table S 4 Patients with a history of immunodeficiency/immunosuppression (incl. corticosteroids): Included patients with a prescription for inactivated varicella zoster (VZ) or pneumococcal vaccine and recorded outcomes

	Inact	ivated VZ vacci	ne	Pneumococcal	vaccine	
	All patients	Patients with outcome	Per 1000 patients	All patients	Patients with outcome	Per 1000 patients
Total	347	10	28.8	848	0	0.0
Females	211	5	23.7	389	0	0.0
Males	136	5	36.8	432	0	0.0
2-17 years	0			160	0	0.0
18-29 years	3	0	0.0	98	0	0.0
30-49 years	13	0	0.0	51	0	0.0
50-59 years	48	0	0.0	114	0	0.0
60-69 years	107	3	28.0	159	0	0.0
70-79 years	115	5	43.5	188	0	0.0
80-89 years	54	1	18.5	69	0	0.0
90-99 years	7	1	142.9	9	0	0.0
Hx VZ	112	9	80.4	68	0	0.0
Hx Z	110	9	81.8	65	0	0.0
No hx VZ	235	1	4.3	780	0	0.0

Table S 5 Patients without a history of immunodeficiency/immunosuppression (incl. corticosteroids): Included patients with a prescription for inactivated varicella zoster (VZ) or live attenuated VZ vaccine and recorded outcomes after the vaccination date

	Inacti	vated VZ vacc	ine	Live attenuated	enuated VZ vaccine	
	All patients	Patients with outcome	Per 1000 patients	All patients	Patients with outcome	Per 1000 patients
Total	2557	35	14.1	1120	2	1.8
Females	1449	20	15.0	602	1	1.7
Males	1103	15	13.0	513	1	1.9
2-17 years	6	0	0.0	757	0	0.0
18-29 years	11	0	0.0	124	0	0.0
30-49 years	52	4	64.5	94	1	10.6
50-59 years	269	4	13.8	27	1	37.0
60-69 years	873	10	11.1	51	0	0.0
70-79 years	942	10	12.2	45	0	0.0
80-89 years	377	4	12.8	22	0	0.0
90-99 years	27	3	96.8	0		
Hx VZ	650	25	40.8	57	2	35.1
Hx Z	641	25	41.4	36	2	55.6
No hx VZ	1907	10	5.0	1063	0	0.0

Table S 6 Patients with a history of immunodeficiency/immunosuppression (incl. corticosteroids): Included patients with a prescription for inactivated varicella zoster (VZ) or live attenuated VZ vaccine and recorded outcomes after the vaccination date

	Inact	ctivated VZ vaccine		Live attenuated VZ vaccine		
	All patients	Patients with outcome	Per 1000 patients	All patients	Patients with outcome	Per 1000 patients
Total	399	11	22.6	153	0	0.0
Females	232	5	17.2	63	0	0.0
Males	157	6	31.8	85	0	0.0
2-17 years	9	0	0.0	76	0	0.0
18-29 years	18	0	0.0	39	0	0.0
30-49 years	17	0	0.0	13	0	0.0
50-59 years	52	0	0.0	6	0	0.0
60-69 years	117	3	25.6	7	0	0.0
70-79 years	122	6	32.8	5	0	0.0
80-89 years	57	1	17.5	6	0	0.0
90-99 years	7	1	142.9	1	0	0.0
Hx VZ	116	9	60.3	11	0	0.0
Hx Z	114	9	61.4	7	0	0.0
No hx VZ	283	2	7.1	142	0	0.0

Table S 7 Patients without a history of immunodeficiency/immunosuppression (incl. corticosteroids): Included patients with a prescription for inactivated varicella zoster (VZ) or pneumococcal vaccine and recorded outcomes after the vaccination date

	Inactiv	ated VZ vacci	I VZ vaccine Pn		Pneumococcal vaccine		
	All patients	Patients with outcome	Per 1000 patients	All patients	Patients with outcome	Per 1000 patients	
Total	2387	37	14.2	4554	5	1.1	
Females	1383	23	14.5	2046	4	2.0	
Males	1004	14	13.9	2491	1	0.4	
2-17 years	0			761	0	0.0	
18-29 years	3	0	0.0	131	0	0.0	
30-49 years	49	4	81.6	159	0	0.0	
50-59 years	259	4	15.4	291	0	0.0	
60-69 years	811	9	11.1	1400	1	0.7	
70-79 years	878	12	11.4	1259	3	2.4	
80-89 years	361	5	11.1	501	1	2.0	
90-99 years	26	3	115.4	52	0	0.0	
Hx VZ	633	28	39.5	264	1	3.8	
Hx Z	625	28	40.0	249	1	4.0	
No hx VZ	1754	9	5.1	4290	4	0.9	

Table S 8 Patients with a history of immunodeficiency/immunosuppression (incl. corticosteroids): Included patients with a prescription for inactivated varicella zoster (VZ) or pneumococcal vaccine and recorded outcomes after the vaccination date

	Inact	ivated VZ vacci	ne	Pneumococcal vaccine		
	All patients	Patients with outcome	Per 1000 patients	All patients	Patients with outcome	Per 1000 patients
Total	347	8	23.1	848	0	0.0
Females	211	4	19.0	389	0	0.0
Males	136	4	29.4	432	0	0.0
2-17 years	0			160	0	0.0
18-29 years	3	0	0.0	98	0	0.0
30-49 years	13	0	0.0	51	0	0.0
50-59 years	48	0	0.0	114	0	0.0
60-69 years	107	3	28.0	159	0	0.0
70-79 years	115	3	26.1	188	0	0.0
80-89 years	54	1	18.5	69	0	0.0
90-99 years	7	1	142.9	9	0	0.0
Hx VZ	112	7	62.5	68	0	0.0
Hx Z	110	7	63.6	65	0	0.0
No hx VZ	235	1	4.3	780	0	0.0

Table S 9 Patients without a history of immunodeficiency/immunosuppression (incl. corticosteroids): Included patients with a prescription for inactivated varicella zoster (VZ) or live attenuated VZ vaccine and recorded outcomes with a diagnosis certainty of 'confirmed'

	Inacti	vated VZ vacc	ine	Live attenuated	VZ vaccine	
	All patients	Patients with outcome	Per 1000 patients	All patients	Patients with outcome	Per 1000 patients
Total	2557	43	16.8	1120	2	1.8
Females	1449	26	17.9	602	1	1.7
Males	1103	17	15.4	513	1	1.9
2-17 years	6	0	0.0	757	0	0.0
18-29 years	11	0	0.0	124	0	0.0
30-49 years	52	4	76.9	94	1	10.6
50-59 years	269	5	18.6	27	1	37.0
60-69 years	873	15	17.2	51	0	0.0
70-79 years	942	12	12.7	45	0	0.0
80-89 years	377	4	10.6	22	0	0.0
90-99 years	27	3	111.1	0		
Hx VZ	650	33	50.8	57	2	35.1
Hx Z	641	32	49.9	36	2	55.6
No hx VZ	1907	10	5.2	1063	0	0.0

Table S 10 Patients without a history of immunodeficiency/immunosuppression (incl. corticosteroids): Included patients with a prescription for inactivated varicella zoster (VZ) or pneumococcal vaccine and recorded outcomes with a diagnosis certainty of 'confirmed'

	Inactiv	vated VZ vacci	ne Pneumococcal		vaccine	
	All patients	Patients with outcome	Per 1000 patients	All patients	Patients with outcome	Per 1000 patients
Total	2387	42	17.6	4554	5	1.1
Females	1383	26	18.8	2046	4	2.0
Males	1004	16	15.9	2491	1	0.4
2-17 years	0			761	0	0.0
18-29 years	3	0	0.0	131	0	0.0
30-49 years	49	4	81.6	159	0	0.0
50-59 years	259	5	19.3	291	0	0.0
60-69 years	811	14	17.3	1400	1	0.7
70-79 years	878	12	13.7	1259	3	2.4
80-89 years	361	4	11.1	501	1	2.0
90-99 years	26	3	115.4	52	0	0.0
Hx VZ	633	33	52.1	264	1	3.8
Hx Z	625	32	51.2	249	1	4.0
No hx VZ	1754	9	5.1	4290	4	0.9