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RESEARCH PAPER

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Trends in herpes zoster epidemiology in Germany based on primary care sentinel surveillance data, 2005–2016

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ABSTRACT

Herpes zoster (HZ) is caused by reactivation of the varicella-zoster-virus (VZV). Childhood varicella vaccination, as recommended in Germany in 2004, may reduce the risk of HZ in vaccinated children but also virus circulation and thus the booster possibility of latent infected persons. In this context we analyzed age-specific trends in HZ epidemiology in Germany using data on HZ-associated outpatient consultations in participating sentinel sites and HZ-associated cases in all hospitals since 2005. We analyzed two separate time periods that differed in sentinel management and data integrity. For the period 2005–2010, we found a decrease in HZ-associated outpatient consultations in 1- to 4-year-olds (IRR = 0.72, 95%CI 0.63-0.81, $p<0.001$). For the period 2013–2016, we observed a decrease in HZ-associated outpatient consultations in 10- to 14-year-olds (IRR = 0.85, 95%CI 0.78-0.93, $p<0.01$). Moreover, we detected an increase in the age groups 20 years and older except for the group 30–39 years. HZ-associated hospitalizations showed similar trends for the second time period (here 2012–2015). The decrease in HZ-associated outpatient consultations and hospitalizations in children started and continued over cohorts eligible for varicella vaccination and could be a result of their reduced HZ-risk. Whether the observed steady increasing HZ incidences for adults are associated with the varicella vaccination in children remains unclear and could not be investigated with our data.

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Background

Herpes zoster (HZ), also known as shingles, is caused by reactivation of the varicella-zoster-virus (VZV). It can occur months to years after initial infection with VZV that causes varicella. The virus persists lifelong in the dorsal roots of the cranial and spinal ganglia of humans.[1] HZ is typically characterized by a painful, blistering rash, generally limited to one dermatome.[1] Severe complications, such as post-herpetic neuralgia, ophthalmic zoster, stroke or other neurological complications occur in up to 30% of patients.[2]

HZ occurs at all ages, yet the highest burden of disease is seen in older adults.[2] The incidence of HZ in Europe ranges from about 1/1,000 in children aged <10 years, to more than 10/1,000 in persons aged 80 years and older.[3] The incidence is distinctly higher in persons from 50 years onwards. Moreover, incidence rates are higher among women than men and this difference increases with age.[3] About 50% of individuals reaching 90 years of age will have had HZ.[4]

A live attenuated vaccine against HZ is licensed in the United States and in Europe. It has an efficacy of 51% in immunocompetent individuals aged ≥60 years which is declining with advancing age.[5] Further, varicella vaccination reduces the risk of HZ in vaccinated children.[6,7] However, it remains unclear, how varicella vaccination influences HZ disease in persons that are latently infected with VZV. The hypothesis on 'exogenous boosting' suggests that VZV immunity gets boosted through repeated exogenous exposure to the wildtype VZV, leading to a decreased risk of developing HZ.[8]

The introduction of universal varicella vaccination in a population leads to a reduction of the number of varicella cases. This might result in fewer possibilities for effective booster contacts and subsequently in an increase of HZ incidence. However, studies and even reviews show conflicting results in this regard.[9,10] In this context of uncertainty it is recommended to maintain monitoring the incidence of HZ in countries either recommending or not varicella vaccination.[9]

In Germany, varicella cases have decreased by 71–88% in the time period 2005–2014[11] after the recommendation of routine childhood varicella vaccination in 2004 (one dose for children aged 11–14 months,[12,13] followed by recommendation of a second dose at age 15–23 months in 2009[14]).

However, there exists neither a national system for HZ surveillance nor any published study on time trends in HZ-associated outpatient consultations in Germany. Statistics on the epidemiology of HZ result mainly from secondary data analyses[15-17] and in one case from a prospective study in one city.[18] The German outpatient sentinel on VZV has provided data on varicella and HZ illness since 2005. Among other things, the data was used for fitting the parameters of a mathematical model on trends in HZ incidence

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and HZ-associated hospitalizations.[19] The model predicted a slow increase for both HZ incidence and HZ-associated hospitalizations in the first 6 years after the recommendation of routine childhood varicella vaccination, followed by a steep increase until the vaccinated cohorts come into older ages (under the assumption that the probability of boosting per infectious contact was 100% and protection thereafter would persist up to 20 years).

The aim of our study was to estimate HZ incidences and to describe age-specific trends over time after introduction of universal varicella vaccination in Germany in order to clarify, whether the expected modeled effect of increasing HZ incidence can be seen in real life.

Results

HZ-cases

A total of 26,621 HZ outpatient-cases were reported between April 2005 and December 2016. During the periods considered for trend analyses, GPs reported 6,538 cases in the first period of 2005–2010 and 10,688 cases in the second period of 2013–2016; pediatricians reported 2,889 cases in 2005–2010 and 1,879 cases in 2013–2016 (Table 1).

Information on age (at least one month of age) was available for 17,225 of the 21,994 cases (78.3%) during the periods considered for trend analyses, which were thus eligible for age-standardized and age group-specific analyses (2005-2010: GPs 3,976 cases, 60.8% of total cases, pediatricians 1,852 cases, 64.1% of total cases; 2013–2016: GPs 9,784 cases, 91.5% of total cases, pediatricians 1,613 cases, 85.8% of total cases). 58% of cases were female, 41% male, and 1% were of missing or unknown sex.

A total of 207,362 hospitalized HZ cases were recorded at all hospitals in Germany from 2005–2015 (Table 1). Overall, 58.2% of hospitalized cases were female.

Crude incidence and trend

The crude HZ consultation incidence rate (C.incidence) based on the total number of HZ cases from outpatient sentinel practices was quite stable in the first time period (between 2.6 and 3/1,000 inhabitants). In the second time period, it increased from 4.0 HZ cases/1,000 inhabitants in 2013 to 4.7 in 2016 (Table 2). Trend analyses using age-standardized incidences based on HZ cases with known age (Table 2) revealed no trend in the first time period but found an increase of 7% per year in the second time period (Table 3).

Overall, the crude number of hospitalized HZ cases per 100,000 inhabitants (H.incidence) increased constantly from 17.5 in 2005 to 28.6 in 2015 (Table 2). The age-standardized H. incidence increased by 3% per year in both time periods of 2005–2010 and 2012–2015 (Table 3).

Age-stratified trends

In the first time period, C.incidence decreased by 28% per year in 1–4 years old ($p<0.001$). In the second time period, C. incidence decreased by 15% in the 10–14 years old ($p<0.001$) and increased in all age groups 20 years and older except 30–39 years, ranging from 5 percent (70-79 years, $p<0.01$) to 13% per year (20-29 years, 40–49 years, $p<0.001$) (Fig. 1a, b, c; Table 3).

In the first time period, H.incidence decreased by 9% per year in the age group 1–4 years ($p<0.01$). It increased for all age groups 5 years and older, ranging from two percent (70-79 years, ≥80 years, $p<0.001$) to seven percent per year (5-9 years, 20–29 years, $p<0.01$). In the second time period, H. incidence decreased by 6 percent for the age group 10–14 years ($p<0.05$) and increased in all age groups between 20 and 79 years, ranging from three percent (60-69 years, $p<0.001$) to eight percent per year (40-49 years, $p<0.001$) (Fig. 2a, b, c; Table 3).

Discussion

Our study is the first trend analysis in countrywide outpatient HZ epidemiology after introduction of universal childhood varicella vaccination in Germany. We are discussing our results in comparison with detected trends in inpatient HZ epidemiology.

Table 1. Sentinel data (total number of outpatient HZ cases by sentinel sites and mean monthly number of participating sentinel sites, by practice type), total number of physicians in practice in Germany (by practice type), number of hospitalized HZ cases, and total population in Germany.

Year	Outpatient HZ cases by sentinel GPs	Participating GPs in the sentinel (mean n/month)	No of GPs in Germany[#]	Outpatient HZ cases by sentinel pediatricians	Participating pediatricians in the sentinel (mean n/month)	No of pediatricians in Germany[*]	Hospitalized HZ cases[#]	Total population[#]
2005	848	210	42,302	416	489	5,687	14,446	82,437,995
2006	1,179	205	41,938	542	471	5,692	15,432	82,314,906
2007	1,188	224	41,438	565	446	5,673	16,705	82,217,837
2008	1,299	249	40,698	528	431	5,686	16,931	82,002,356
2009	1,111	222	40,094	466	402	5,726	17,317	81,802,257
2010	913	161	39,568	372	355	5,720	18,436	81,751,602
2011	1,457	209	38,928	666	423	5,730	19,558	80,327,900
2012	1,801	246	38,302	703	450	5,759	20,470	80,523,746
2013	2,896	345	37,682	601	480	5,761	21,586	80,767,463
2014	2,573	294	36,947	540	455	5,770	23,018	81,197,537
2015	2,435	252	36,164	409	416	5,738	23,463	82,175,684
2016	2,784	262	36,164[§]	329	402	5,738[§]	—	82,175,684[§]

HZ: Herpes zoster.
[#]Data derived from the information system of the Federal Statistical Office.
[*]Data derived from the information system of the Federal Health Monitoring.
[§]As data was only available for the years until 2015, we used the data from 2015 for 2016 accordingly.

Table 2. Crude and age-standardized annual outpatient consultation incidence (C.incidence) and hospitalization incidence (H.incidence) with 95% confidence interval (95%CI).

Year	Crude C.incidence (95%CI) per 1,000 population*	Age-standardized C.incidence (95%CI) per 1,000 population#	Crude H.incidence (95%CI) per 100,000 population	Age-standardized H.incidence (95%CI) per 100,000 population
2005	—	—	17.52 (17.24–17.81)	18.19 (17.9–18.5)
2006	3.01 (2.99–3.02)	1.99 (1.98–2.00)	18.75 (18.45–19.05)	19.17 (18.9–19.5)
2007	2.87 (2.86–2.88)	1.90 (1.89–1.91)	20.32 (20.01–20.63)	20.49 (20.2–20.8)
2008	2.71 (2.70–2.73)	1.87 (1.87–1.88)	20.65 (20.34–20.96)	20.47 (20.2–20.8)
2009	2.61 (2.59–2.62)	1.66 (1.65–1.67)	21.17 (20.86–21.49)	20.61 (20.3–20.9)
2010	2.91 (2.90–2.93)	2.13 (2.12–2.14)	22.55 (22.23–22.88)	21.66 (21.3–22.0)
2011	3.50 (3.49–3.52)	2.38 (2.37–2.40)	24.35 (24.01–24.69)	23.19 (22.9–23.5)
2012	3.60 (3.59–3.61)	2.54 (2.53–2.55)	25.42 (25.07–25.77)	23.97 (23.6–24.3)
2013	3.96 (3.95–3.98)	3.47 (3.45–3.48)	26.73 (26.37–27.09)	24.92 (24.6–25.3)
2014	4.03 (4.02–4.05)	3.65 (3.64–3.67)	28.35 (27.98–28.72)	26.17 (25.8–26.5)
2015	4.26 (4.24–4.27)	3.84 (3.83–3.85)	28.55 (28.19–28.92)	26.38 (26.0–26.7)
2016	4.66 (4.65–4.68)	4.25 (4.24–4.27)	—	—

*based on the total number of herpes zoster cases.
#based on herpes zoster cases with known age.

Moreover, we compare our findings with trends derived from mathematical modeling, as well as with findings from other countries.

In the first years after the recommendation of routine childhood varicella vaccination, we observed stable incidences in overall HZ-associated outpatient consultations and an increasing trend in HZ-associated hospitalizations. Thus, only hospital data reflected the slow increase in the first five years following vaccine introduction that was also estimated by a model.[19] Mathematical modelling further predicted a steep increase of up to 20% in outpatient consultations in the following 10 years and of up to 24% in hospitalizations in the following 20 years.[19] Our results showed increasing trends in the second time period (starting 2012/2013) for both, consultation and hospitalization incidences, to an extent comparable to the model estimations. However, the increase in hospitalization incidence occurred continuously over the total observation time and was previously shown to have started already before varicella vaccination was introduced in the German childhood vaccination schedule.[20] Thus, our HZ hospitalization trends do not confirm the predicted course, whereas the observed steep increase in HZ-associated outpatient consultations corresponds to the model estimations, particularly regarding adults aged 20 years and older. Unfortunately, a change in sentinel management and data integrity in 2011/12 hampered a reliable and continuous trend analysis of sentinel data over the whole time period 2005–2016.

In other countries with childhood varicella vaccination, the increase in HZ incidence had also started before childhood varicella vaccination was introduced and was seen for outpatient consultations[21-33] as well as for hospitalizations.[34] This finding suggests that factors other than exogenous boosting could be responsible for the increase in HZ incidence. In reviews regarding exogenous boosting, authors came to inconclusive results. Either available data was insufficient to confirm an impact of routine childhood varicella vaccination on the HZ incidence[9] or the authors concluded, that exogenous boosting may exist but not for all persons or situations.[10] In a recent study, T-cell immunity and VZV-specific antibodies were boosted in only 17–25% of older adults after a re-exposure to varicella. Moreover, the booster effect lasted only for less than one year.[35]

Our results will inform the Standing Committee on Vaccination (STIKO) in Germany on trends in HZ epidemiology that are of interest for two reasons: Firstly the STIKO is re-evaluating its recommendations on varicella childhood vaccination among other aspects also with regard to the possible impact of this vaccination on HZ epidemiology. Secondly a new adjuvanted recombinant subunit HZ vaccine[36] was licensed in the USA in 2017. This might restart the discussion about recommendation of HZ vaccination in Germany, as the live

Table 3. Trends for outpatient consultation incidence (C.incidence) and hospitalization incidence (H.incidence), age-stratified and overall, given by incidence rate ratios per year (IRR, 95% CI, p-value) for two time periods (first time period: 2005–2010, second time period: 2013–2016 for C.incidence and 2012–2015 for H.incidence)

	C.Incidence (2005-2010)		H.Incidence (2005-2010)		C.Incidence (2013-2016)		H.Incidence (2012-2015)	
Age group	IRR (95%CI)	p-value	IRR (95%CI)	p-value	IRR (95%CI)	p-value	IRR (95%CI)	p-value
<1 year	1.03 (0.61–1.75)	0.91	0.83 (0.69–1.01)	0.06	0.66 (0.20–2.17)	0.49	0.80 (0.55–1.15)	0.23
1-4 years	0.72 (0.63–0.81)	<0.001	0.91 (0.85–0.97)	<0.01	0.98 (0.71–1.34)	0.90	0.96 (0.83–1.11)	0.57
5-9 years	0.95 (0.87–1.04)	0.26	1.07 (1.02–1.11)	<0.01	0.87 (0.76–1.00)	0.05	0.93 (0.85–1.02)	0.13
10-14 years	1.07 (0.98–1.16)	0.15	1.04 (1.01–1.08)	<0.05	0.85 (0.78–0.93)	<0.001	0.94 (0.88–1.00)	<0.05
15-19 years	0.94 (0.84–1.05)	0.28	1.04 (1.01–1.08)	<0.05	1.08 (0.96–1.20)	0.19	0.98 (0.93–1.04)	0.55
20-29 years	1.07 (0.95–1.21)	0.26	1.07 (1.04–1.09)	<0.001	1.13 (1.05–1.22)	<0.001	1.05 (1.01–1.08)	<0.01
30-39 years	1.08 (0.96–1.21)	0.19	1.06 (1.04–1.08)	<0.001	1.06 (0.99–1.15)	0.09	1.07 (1.04–1.10)	<0.001
40-49 years	1.02 (0.94–1.10)	0.65	1.06 (1.05–1.08)	<0.001	1.13 (1.07–1.19)	<0.001	1.08 (1.05–1.11)	<0.001
50-59 years	1.02 (0.97–1.07)	0.46	1.03 (1.02–1.04)	<0.001	1.06 (1.01–1.11)	<0.05	1.04 (1.03–1.06)	<0.001
60-69 years	0.98 (0.94–1.02)	0.34	1.03 (1.01–1.05)	<0.001	1.09 (1.04–1.14)	<0.001	1.03 (1.01–1.04)	<0.001
70-79 years	1.02 (0.98–1.06)	0.36	1.02 (1.02–1.03)	<0.001	1.05 (1.02–1.09)	<0.01	1.06 (1.04–1.07)	<0.001
≥80 years	0.98 (0.91–1.06)	0.61	1.02 (1.02–1.03)	<0.001	1.07 (1.01–1.12)	<0.05	1.01 (1.00–1.02)	0.11
Overall	1.01 (0.99–1.03)	0.45	1.03 (1.02–1.05)	<0.001	1.07 (1.04–1.10)	<0.001	1.03 (1.02–1.05)	<0.001

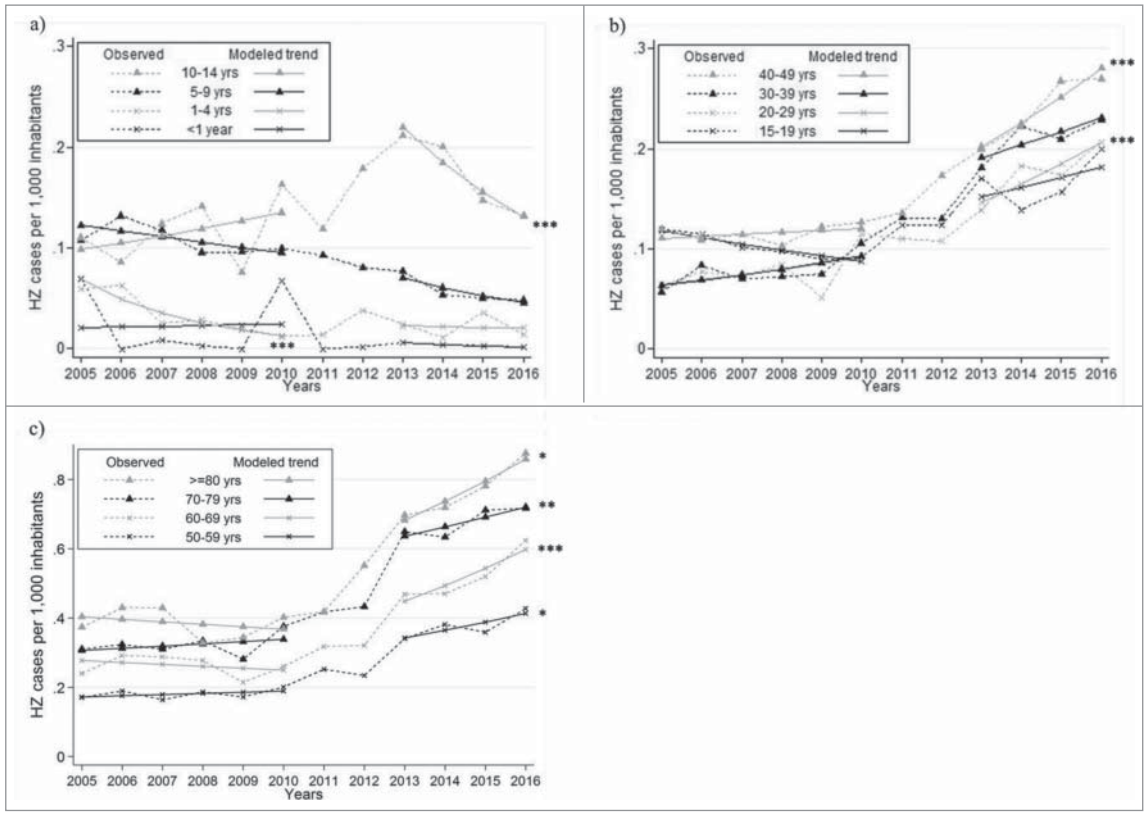

Figure 1. Yearly mean of monthly outpatient HZ cases per 1,000 inhabitants per age group, data for 2005–2016 and modeled trends for 2005–2010 and 2013–2016. a) age groups <15 years, b) age groups >14 and <50 years, c) age groups ≥50 years ($^{*}p<0.05$, $^{**}p<0.01$, $^{***}p<0.001$).

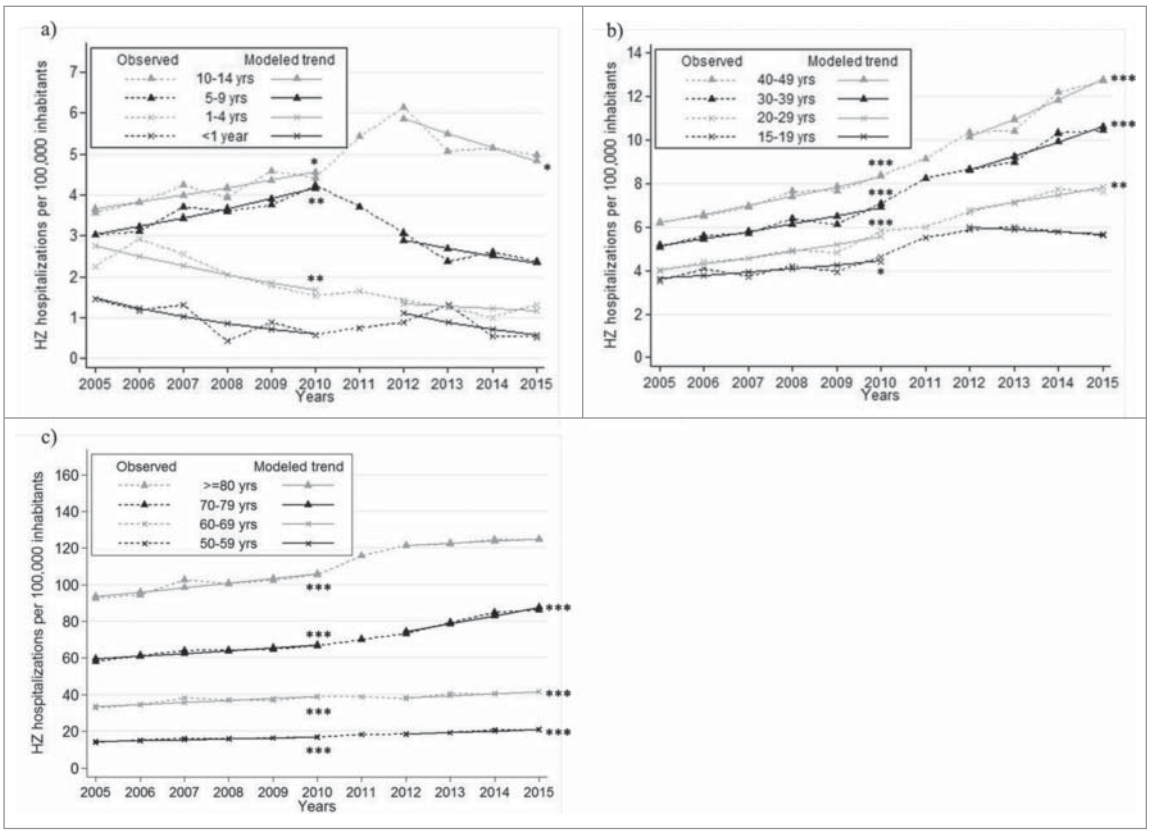

Figure 2. HZ-associated hospitalizations per 100,000 inhabitants per age group, data for 2005–2015 and modeled trends for 2005–2010 and 2012–2016. a) age groups <15 years, b) age groups >14 and <50 years, c) age groups ≥50 years ($^{*}p<0.05$, $^{**}p<0.01$, $^{***}p<0.001$).

attenuated vaccine against HZ is not recommended by the STIKO "based on the conclusion, that an effective and sustainable reduction of the HZ disease burden cannot be achieved with this vaccine".[37]

We found no other study on temporal trends in HZ-associated outpatient consultations outside of Germany, which distinguished age groups in children in the same detail. A study in Antelope Valley, California, USA, detected a decrease in HZ-associated outpatient consultations in children less than 10 years of age. The decrease was observed in the period from 2000 to 2010, when universal varicella childhood vaccination in the USA had already been established.[28] In contrast, another US-study could detect no trend from 1992 to 2002, while covering a period shortly before and after introduction of varicella childhood vaccination.[38] Likewise, we would have missed trends in HZ-associated outpatient consultations in children, if we had only regarded the wider age group of children <10 years (data not shown).

In the first period analyzed for our study (2005-2010), HZ-incidences decreased in children 1–4 years of age, both in outpatient and in hospital data. However, we detected no further significant decrease in the following time period. Further analysis revealed a decreasing trend in H.incidence in 5- to 9-year-olds from 2010 onwards (data not shown) and in the 10- to 14-year-olds from 2013 onwards which was also seen in outpatients. The incidence decrease in certain age groups seems plausible considering that it started and proceeded in cohorts eligible for varicella vaccination. It could therefore be a result of the reduced HZ-risk in these cohorts, as virus strains of vaccine-type are less likely to reactivate than wild-type strains.[6,7,39,40] Our findings regarding HZ-associated hospitalizations expand the findings of Siedler and Dettmann,[20] who analyzed the time period 1995 to 2012. They already discussed a decrease in the H. incidence in 5- to 9-year-olds, but could not confirm it at that time.

Yet, it has to be noted that trends were defined by statistical criteria and were partly based on very low incidence rates, especially in all groups below 50 years of age.

The overall crude C.incidence observed in our study was lower compared to another study in Germany based on secondary data analyses.[15] However, only GPs and pediatricians reported HZ cases in our study, whereas in the other study all physician groups were included. Trends in our study could have been biased, if the consultation behavior of HZ patients had changed during the study period. We did not find any information on this. Further limitations are (1) that we cannot verify representativeness and rule out selection bias, as participation in the sentinel was voluntary. We sought representativeness by recruiting a high proportion of participating sentinel sites and taking care of a good regional coverage. Thus, we received monthly reports from 6.4 to 8.9% of all pediatricians and 0.5 to 0.7% of all GPs in each of the six regions. (2) For the calculation of incidence rates we assumed that the population covered by participating practices is representative for the population covered by the total of all practices in Germany. However, this cannot be proven as patients in Germany are not assigned to certain GP or pediatric practices, but are free to choose a physician. (3) A change in sentinel management led to improved data quality resulting in a higher proportion of cases with available information on age in the datasets since 2013. HZ-cases without information on age could not be considered in the numerator for the calculation of age-stratified practice indices (PIs). Yet, a sentinel practice was counted in the denominator if at least one single case report was provided in this month. Thus, missing cases because of unknown age led to decreased PIs compared to the real value. With improving data integrity we cannot rule out that this phenomenon boosted an increase or diminished a decrease. To account for this, we analyzed the two time periods before and after the change in sentinel management separately and used the hospitalization data for validation. (4) A causal relationship between the varicella vaccination and the HZ-incidence increase in adults cannot be proven with ecological data.

Conclusions

The incidence decrease in children after recommendation of varicella vaccination seems plausible considering a reduced HZ-risk of children in cohorts eligible to the recommended varicella vaccination. A causal relationship between varicella vaccination in children and the observed incidence increase in adults remains unclear and cannot be proven with the used data.

The evaluation of effects of childhood varicella vaccination has to include effects on the occurrence of HZ in vaccinated persons and in persons latently infected with VZV. Appropriate surveillance of HZ is necessary to detect trends of HZ by age or by groups at particular risk for HZ and is essential regarding HZ vaccination. Sentinel surveillance is a possible tool, however data integrity and representativeness have to be ensured.

Methods

We used outpatient data derived by active sentinel surveillance as well as inpatient data by hospital admissions statistics. The aim was to detect trends of HZ incidence overall and in 12 age groups (under 1 year of age, one to four years, five to nine years, ten to 14 years, 15 to 19 years, 20–29 years, 30–39 years, 40–49 years, 50–59 years, 60–69 years, 70–79 years, and 80 years and more).

HZ-associated outpatient consultations were assessed using data from April 2005 until December 2016 from the AGV sentinel (working group on varicella, *[Arbeitsgemeinschaft Varizellen]*). The AGV sentinel was established in April 2005 to investigate the influence of the varicella vaccination on the occurrence of varicella and HZ in the German population and is described in detail elsewhere.[41] It is based on voluntary participation of physicians who were asked to monthly report the number of HZ cases in a summary report (including zero cases) and to complete a single case report for each HZ case. The single case reports include the patient's gender and age.

We calculated crude C.incidences using the total number of reported HZ cases from both reporting forms. If the sum of monthly HZ cases per practice according to the summary report did not match the sum of single case reports of the same practice, we considered the higher number of HZ cases. Overall age-standardized and age-stratified trend analyses were based on the HZ cases according to the single case reports.

Age was calculated as difference between month and year at birth and month and year of first HZ-consultation. As this may lead to a possible variation of one month in age and as infantile HZ is a rather rare event, we excluded cases with age below one month.[42,43] We analyzed two time periods separately, 2005–2010 and 2013–2016, that differed in sentinel management and data integrity: In the first time period the sentinel was managed in public-private-partnership by the Robert Koch Institute (RKI) as the German national public health institute, the German Green Cross ("Deutsches Grünes Kreuz", DGK), and vaccine manufactures who financed the work of the DGK. While the RKI gave scientific guidance and analyzed the data, the DGK was responsible for the recruitment of physicians and data collection.[41,44] Starting in April 2011, the project was shifted into the sole responsibility of the RKI, financed by the Federal Ministry of Health, and this transition was finished in 2012. In order to account for decreasing numbers of participating sentinel practices, recruitment calls were launched in 2011 and in 2012. Data integrity, measured by the proportion of cases with information on age available from all HZ cases reported, improved markedly from 2013 onwards. We analyzed the two periods each with a stable management of participants and data and left out the transition time.

Outpatient consultation incidence

Patients in Germany can choose the physician to be contacted for each consultation and we do not know how many persons are cared for by a sentinel physician. Thus, we calculated the C.incidence based on the method proposed by Uphoff and Stilianakis et al. 2000.[45] This method assumes, that the population covered by participating practices is representative for the population covered by all other practices in Germany.

In a first step, we calculated the monthly practice index (PI) as the number of reported HZ cases divided by the number of practices that provided reports in the respective month. For the analysis of crude C.incidences, we calculated the monthly PI using the total number of HZ cases and all practices that provided any report (monthly reports including those with zero cases and/or single case reports). For overall age-standardized and age-stratified trend analyses, we calculated the montly PI using single case reports stratified by age group. We used all practices which provided single case reports or summary reports with zero cases (and no single case reports) as the denominator. The PI was calculated separately for two groups, GPs and pediatricians, as the number of HZ cases between practices caring for adults (mainly GPs, internists in general practice) and children (mainly pediatricians) differs strongly. In order to address the regional variation of practices providing monthly reports, the PI was further stratified into six regions with similar population size: Region North (Bremen, Hamburg, Lower Saxony, Schleswig Holstein), Region East (Berlin, Brandenburg, Mecklenburg Western Pomerania, Saxony, Saxony-Anhalt, Thuringia), Region West 1 (Hesse, Rhineland-Palatinate, Saarland), Region West 2 (North Rhine-Westphalia), Region South-West (Baden-Wuerttemberg), and Region South-East (Bavaria).

In a second step, we projected the monthly HZ cases per practice to the total number of HZ cases occurring in the region. This was determined by multiplying the regional PIs with the number of physicians in the respective region (separately for GPs and pediatricians).

In a third step, we summed the projected regional numbers up to obtain the total number of HZ cases in Germany. The monthly outpatient consultation incidence per 1,000 persons was determined by dividing the projected number of HZ cases by the number of the German population times 1,000.

$$Consultation\ incidence_m = \frac{\sum_{r=1}^{6}\sum_{p=1}^{2} PI_{prm} * N_{prm}}{Population_m} \times 1,000$$

p: practice type (1: GP, 2: pediatrican)
r: region
m: month
PI_{prm}: practice index per practice type, region, and month
N_{prm}: Number of physicians active in primary care per practice type, region, and month
$Population_m$: monthly population = population in the respective year

For the presentation of yearly crude C.incidences, we calculated the yearly C.incidences by adding the respective monthly C.incidences. For the presentation of yearly age-stratified C.incidences, we applied the formula separately for each age group. We calculated the yearly mean of monthly HZ cases/1,000 inhabitants by adding the monthly C.incidences and dividing it through the available months (9 in 2005, otherwise 12).

The number of practicing physicians in Germany in the two physician groups was derived from the information system of the Federal Health Monitoring.[46] The population statistics were derived from the information system of the Federal Statistical Office.[47] As both were only available for the years until 2015, we used the data from 2015 for 2016 accordingly.

We compared the overall crude C.incidences based on the total number of HZ cases with the results of other incidence studies in order to evaluate the reliability and applicability of the sentinel data. We used the age-standardized and the age-stratified C.incidences for trend analyses only. They were based on the limited number of HZ single case reports with known age, and were thus not assumed to reflect the real incidences.

Hospitalization incidence

Data on HZ-associated hospitalizations were available from 2005 until 2015 from the information system of the Federal Statistical Office.[48] We calculated annual total (crude and age-standardized) and age-stratified H.incidences based on all patients with a primary diagnosis of HZ (ICD10 codes B02.x). The H.incidences were used to compare and verify trends observed in the C.incidences. Therefore, we conducted trend analyses separately, but in the comparable time periods 2005–2010 and for the last four years of the available data (here 2012–2015).

Statistical analyses

For the annual crude C.incidences and H.incidences we estimated Poisson 95%CIs. Annual age-standardized C.incidences

and H.incidences were calculated per 100,000 of the total European Standard population (ESP) 2013 taking into account the age groups according to the ESP.[49] For trend analyses, we derived the incidence rate ratio (IRR) with 95%CI by using negative binomial regression. We conducted trend analyses for C. incidences with monthly HZ cases as dependent variable, year as continuous independent variable, and population size as the exposure variable. Trend analyses for H.incidences were conducted with annual hospitalized HZ cases as dependent variable, year as continuous independent variable, and population size as the exposure variable. A p-value <0.05 was considered as statistically significant.

All analyses were performed with Stata for Windows, version 14 (StataCorp, College Station, TX).

Disclosure of potential conflict of interest

There are no potential conflicts of interest to be declared.

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