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11 **Complications of Varicella after Implementation of Routine Childhood Varicella**
12 **Vaccination in Germany**

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surveillance system

Abbreviated title: Varicella complications in Germany

Running head title: Varicella complications in Germany

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Abstract

1
2 A country-wide sentinel surveillance system was initiated in Germany after
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4 implementation of routine varicella vaccination of children >11 months. Sentinel
5
6 physicians report monthly the number of cases and of severe varicella complications
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8 (VC). Case-based questionnaires are completed for VC. We evaluated trend and
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10 clinical features of reported VC from April 2005 to March 2009. Reported VC
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12 decreased by 81%.
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Introduction

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2 Although varicella is commonly regarded as a mild disease, serious complications
3 and death occur (2). In Germany, up to June 2004 vaccination against varicella was
4 only recommended for special risk groups and their contacts and as post-exposure
5 prophylaxis. Universal varicella vaccination of all children 11-14 months of age was
6 recommended by Germany's Standing Committee on Vaccination in July 2004 (6).

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15 The main objective of this recommendation was reduction of morbidity, and varicella
16 complications and consequently, the economic burden of disease (5). Varicella is not
17 notifiable in Germany. Countrywide varicella sentinel surveillance was initiated¹ in
18 April 2005 to evaluate the effects of vaccination. Operative details of the sentinel
19 system have been described elsewhere (7).

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27 This report describes frequency and type of severe varicella complications (VC)
28 found in four years of sentinel surveillance.
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Methods

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38 The sentinel consists of a countrywide convenience sample of more than 1,000
39 primary care physicians, of whom 60% are paediatricians and 40% general
40 practitioners (GP). The relative geographic distribution of the sentinel physicians is
41 comparable to the total number of active physicians (~1% of GPs and ~15% of all
42 paediatricians in each region). Participation is voluntary, no incentives are given.
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Questionnaires include case definitions: A case of varicella is defined as a person presenting with a typical clinical picture of maculo-papulo-vesicular rash on skin or mucosa. A severe varicella complication (VC) is defined as varicella leading to hospitalization, resulting in oral or parenteral antibiotic or antiviral therapy or accompanied by neurologic symptoms. We analyzed the frequency and type of VC within the sentinel system in four consecutive seasons (April until March of the following year).

For data entry and management MS Access 2007[®] was used, MS Excel 2007[®] and Stata[®] version 10 (StataCorp LP, Texas, USA) were used for data analysis.

Consistency checks were performed by comparing single case reporting of VC via case-based questionnaire with the total number of VC cases reported via monthly questionnaire. Using Pearson chi-squared test statistically significant differences were determined. All p-values are two-sided and the significance level set at $p < 0.05$.

Results:

From April 2005 to March 2009, 83,075 varicella cases were reported in monthly questionnaires by 1,176 sentinel physicians. While participation of sentinel physicians remained stable, the number of reported varicella cases as well as of VC decreased by 63% and 81%, respectively, when comparing the 4th to the 1st season. Cases of varicella and VC peaked in spring.

Overall, 280 VC were reported via case-based questionnaires (10% less than in the monthly figures) by 150 physicians, corresponding to 0.34% of all reported varicella cases. Decrease in VC was highest (83%) in the age-groups 0-4 and 5-9 years.

1 Most VC occurred in 0-4 (59%) and 5-9 (31%) year olds, 126 (48%) in males. Of all
2 reported varicella cases the highest proportion of complications occurred in children
3 younger than 2 (24%) and adults older than 20 (5%) years old.
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6
7 The type of complication could be identified in 278 VC patients: 144 dermatologic, 27
8 neurologic and 127 other complications (Table 1). Twenty VC patients had more than
9 one type of complication. Bacterial superinfections (n=108, 36% of VC and 0.13% of
10 all reported varicella cases, respectively) were most common among skin
11 complications, followed by phlegmon (spreading diffuse inflammatory process with
12 formation of pus, n=15, 5% of VC) and abscess (localized, cavity formed and
13 drainable infected fluid collection, n=9, 3% of VC). Among "other complication" 47
14 cases had otitis media (16% of VC and 0.06% of all varicella cases, respectively) and
15 21 had pneumonia (7% of all VC). Neurologic complications accounted for 0.03% of
16 all varicella cases (n=27, 9% of all VC). A decline in the number of complications
17 over time was observed in all 3 reported categories, but was greatest for skin and for
18 other complications.
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37 Underlying conditions were reported in 30 (11%) VC cases, in three more than one
38 condition was present: Twelve patients had atopic dermatitis, 11 had chronic
39 diseases such as bronchial asthma, diabetes mellitus, dismorphic syndrome with
40 retarded growth, coronary fistula, multifocal pneumonia with residual bronchitis,
41 nephrocalcinosis, valvular and aortal stenosis, epilepsy and anemia. Six patients had
42 underlying immune-compromising conditions and four were oncology patients. The
43 type of VC did not differ between previously healthy and patients with underlying
44 conditions, but the latter were hospitalised more often (34.0% vs. 27.0%) and
45 showed permanent sequelae more often (16.7% vs. 6.4%) ($p>0.05$).
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Seventy-one VC cases were hospitalised (median age 3 years). Patients with neurologic VC were hospitalized more often than patients with dermatologic or other VC (56% vs. 21% and 24%, respectively).

In 94 cases (33%) the outcome remained unknown, 165 (59%) recovered completely, 19 (7%) developed permanent sequelae and two patients died

Comparison of those having permanent sequelae or death (n=21) with those who fully recovered (n=165) showed no significant difference by gender, age-groups, complications type and vaccination status.

Of 277 VC with known vaccination status 16 (5.8%) were vaccinated, none of them twice. In six cases varicella presented within 42 days after vaccination, suggesting vaccination within the incubation period or vaccine related varicella. Ten cases occurred more than 42 days after vaccination (breakthrough cases): five presented with otitis media (one combined with bronchitis and one with balanitis) and two with bacterial superinfection. Three patients had other complications, two of whom were hospitalized because of dehydration and nephrotic syndrome.

Discussion

Our results give the first assessment of severe varicella complications after the introduction of universal varicella vaccination in Germany. Studies estimating the burden of VC before introduction of universal childhood varicella vaccination have relied mostly on hospital data (1;4;8;9).

Our findings are are similar to those of Ziebold et al. (9), who demonstrated in a one year survey of children younger than 16 years within pediatric hospitals in Germany that the majority of complications occurred in pre-school aged children, especially in those less than 1 year of age.

1 Among hospitalized VC patients reported, the median age was comparable to that
2 estimated by capture-recapture analysis by Liese et al. (3;4) before universal
3 varicella vaccination was available in Germany. In this study, an underlying chronic
4 disease was reported in 23% of hospitalized cases, in contrast to 14% among the
5 hospitalized cases reported in the sentinel. However, in both studies the majority of
6 patients with VC or who were hospitalized related to VC were previously healthy
7 persons. This supports the general recommendation for varicella vaccination in
8 childhood rather than a vaccination targeted only at risk groups.
9

10 Within the sentinel, the proportion of VC was smaller than estimated by Wutzler et al.
11 (8) in a combined seroepidemiologic and analytic study. Possibly our results do not
12 reflect the true proportion because very severe cases present directly at the hospital
13 and are not retrospectively reported by the sentinel physician. Furthermore,
14 physician-based surveillance is known to be affected by reporting bias, possibly
15 leading to underreporting.
16

17 The total number of varicella cases and reported complications within the sentinel
18 decreased over time with increasing vaccine uptake (11). The overall number of VC
19 is low, confirming the success of the varicella vaccination program in Germany. Long
20 term consequences of routine varicella vaccination cannot be determined with the
21 use of our sentinel data. Population based surveillance programs should be
22 established in the future to monitor further the impact of varicella vaccination on the
23 epidemiology of varicella infections.
24

25 **Acknowledgements**

26 We would like to acknowledge participating physicians of the working group for
27 measles and varicella (AGMV) for their contributions to the varicella surveillance in
28

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Figure legends:

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Figure 1: Proportion of varicella complications among all varicella cases reported within the varicella sentinel surveillance system in Germany, 2005-2009

Figure 2: Decrease of varicella complications within the varicella sentinel surveillance system in Germany, 2005-2009

Figure 3: Varicella complications by age-groups and by gender within the varicella sentinel surveillance system in Germany, 2005-2009

Figure 4: Proportion of varicella complications among all varicella cases reported by age-groups within the varicella sentinel surveillance system in Germany, 2005-2009

Table 1: Varicella complications by type, underlying conditions and hospitalisation status within the varicella sentinel surveillance system in Germany, 2005-2009

complications	total			previously healthy		underlying conditions		hospitalised
	N=278 +20 [#]	%	median age	N=250+ 17 [#]	%	N=28+ 3 [#]	%	
Patients								N=69+ 7 [#]
skin	144	48.3		126	47.2	18	58.1	30
bacterial superinfections	104	34.9	3.5	90		12		18
phlegmona	13	4.4	4	11		2		5
abscess	7	2.3	2	6		1		2
superinf. with phlegmona	2	0.7	5	2		0		0
superinf. with abscess	2	0.7	3	2		0		0
*other skin infection	16	5.4	3	13		3		5
neurological	27	9.1		27	10.1	0	0	15
cerebellitis	7	2.3	5	7		0		4
encephalitis	6	2.0	5	6		0		4
meningitis	1	0.3	0	1		0		1
§other neurol. compl.	13	4.4	5	13		0		6
other complications	127	42.6		114	42.7	13	41.9	31
otitis media	47	15.8	4	46		1		2
pneumonia	20	6.7	4	17		3		7
arthritis	5	1.7	3	4		1		1
hemato-oncologic sympt.	4	1.3	4.5	4		0		4
pneumonia with hemato-oncologic symptoms	1	0.3	20	1		0		1
§further VC	50	16.8	4	42		8		16

[#]multiple nominations * conjunctivitis, blepharitis, erysipel, impetigo etc. § facial paresis, tinnitus, hyperreflexia etc. § lymphadenitis, keratinitis etc.

Figure 1
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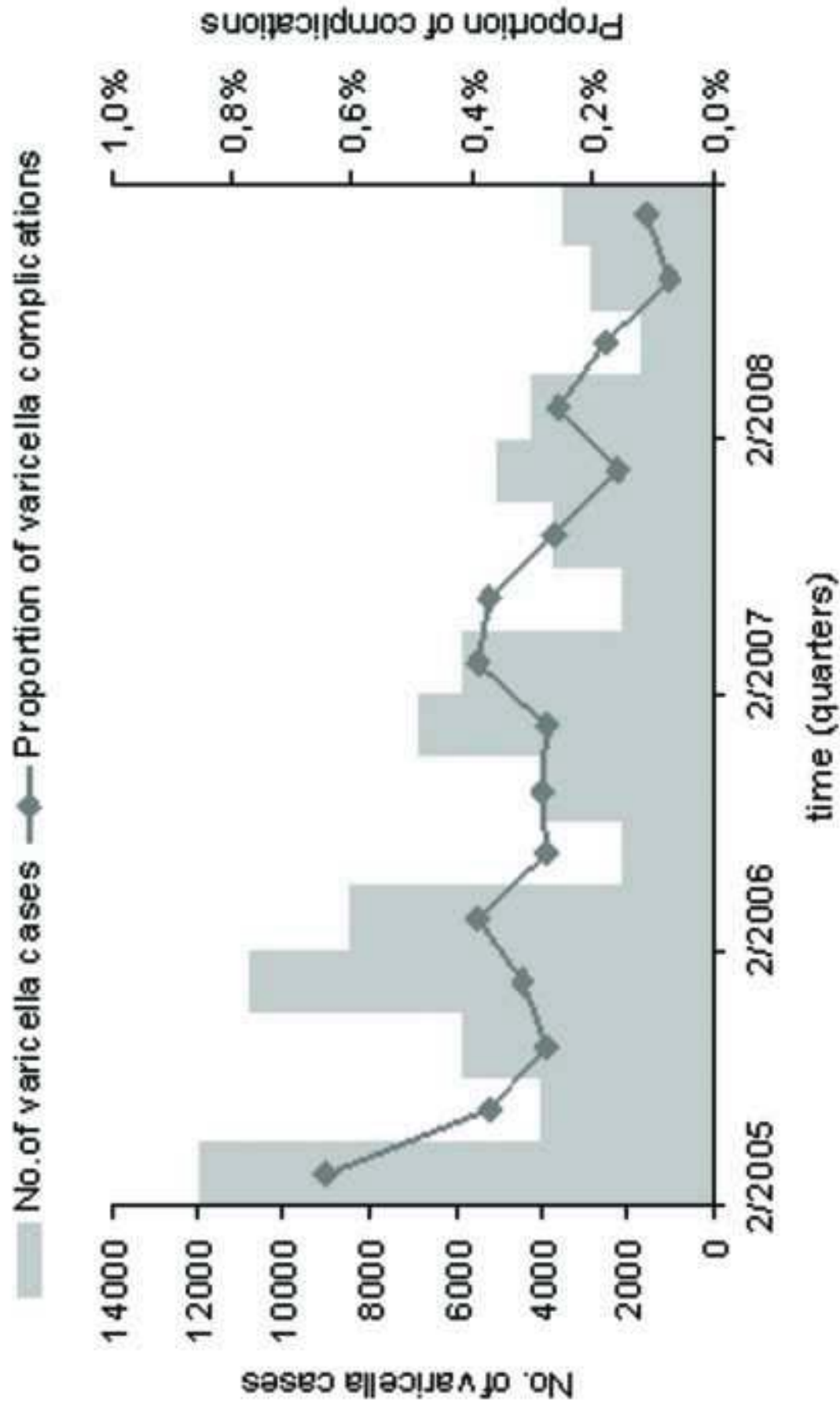


Figure 3
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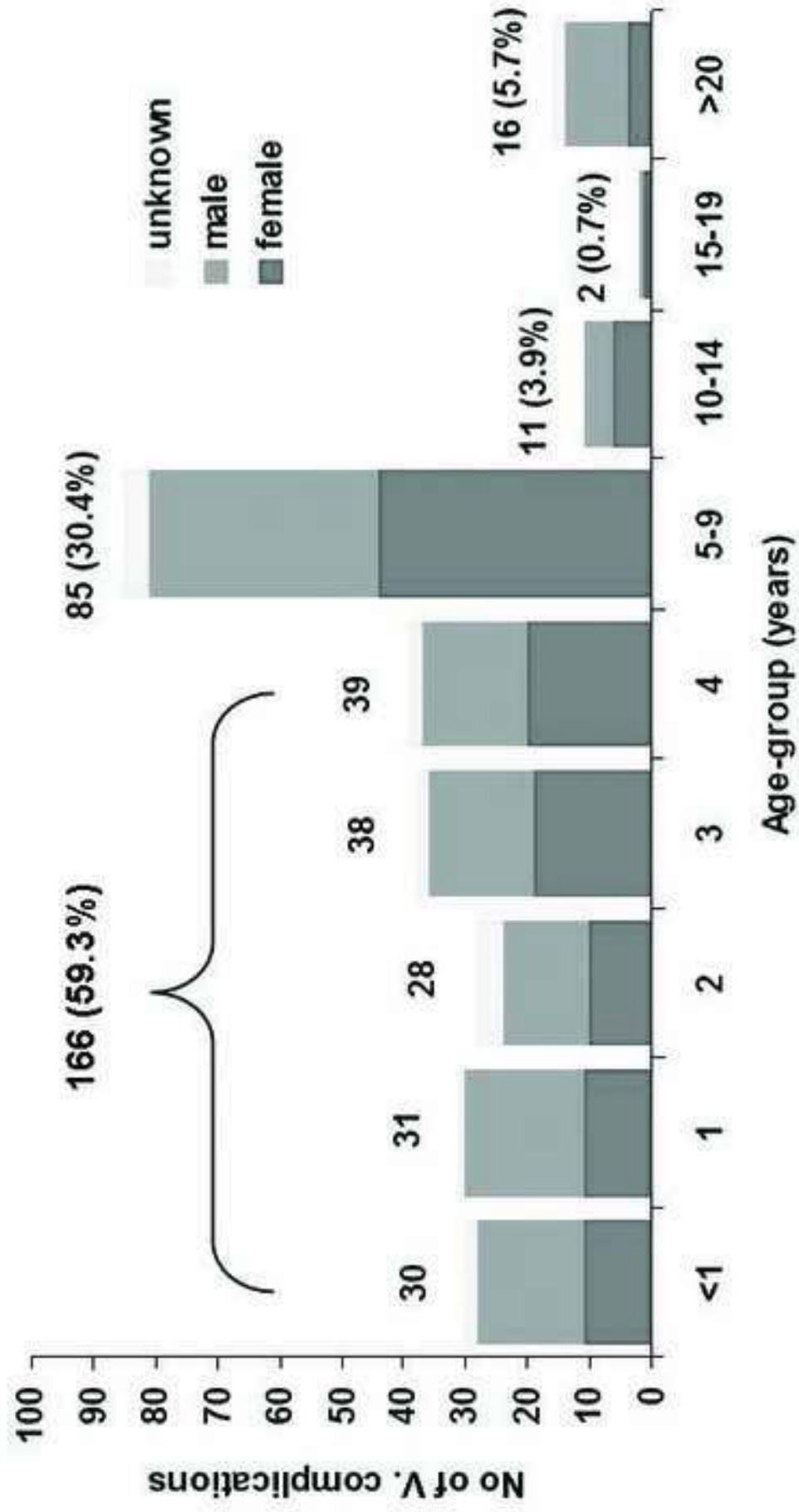


Figure 4
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