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The incidence of influenza-associated hospitalizations in children in Germany

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SUMMARY

Since new vaccines and anti-viral drugs for influenza have become available, collation of actual and country-specific epidemiological data is essential. Since respiratory syncytial virus (RSV) is a well known paediatric airway pathogen and some epidemiological data exist already, a comparison between influenza and RSV seems warranted. From July 1996 to June 2001 the naso-pharyngeal aspirates (NPA) of children from birth to 16 years of age, admitted to one of the two paediatric hospitals in Kiel, Germany, were investigated by a nine-valent multiplex reverse transcriptase PCR assay. NPA were investigated in 60·8% of 3469 children admitted with an acute respiratory tract infection. Community-acquired or nosocomial infections (in parentheses) due to influenza A were diagnosed in 122 (10) children, due to influenza B in 14 (2) and due to RSV in 325 (24) cases. Patients with influenza A (median 752 days) and influenza B (median 966 days) were older than patients with RSV (median 168 days). The spectrum of disease presentation was broader in influenza than in RSV. In each winter, admissions with influenza were less common than those with RSV. Influenza B only occurred in 2 of the 5 years. The cumulative, population-based incidences per 100 000 children 0–16 (0–5, >5–16) years of age were 53 (123, 22) for influenza A, 16 (30, 9) for influenza B and 165 (453, 4) for RSV. Cardiac conditions and asthma were the major risk factors for admission to hospital with influenza A (RR 9·8, 4·1) and RSV (8·5, 2·1) infections. Underlying conditions were most common in influenza B. Low gestational age doubled the risk for admission to hospital with influenza A infection, but did not show a dose–effect relationship as in RSV. The burden of influenza-positive hospitalizations was about one third that of RSV. The incidence was similar to reports from the United States. Targeting children with underlying conditions, especially cardiac conditions and asthma in the German immunization programme is appropriate, as long as no policy for vaccination of the general paediatric population exists.

INTRODUCTION

Acute respiratory tract infections (ARI) contribute most to the overall burden of disease [1]. They are of high impact in children on the direct burden of disease as well as mediating the yearly epidemic efficiently to the adult segment of the population [2, 3]. For Germany, no precise population-based data or pathogen-specific data on the epidemiology of influenza exist so far. At present, the German vaccination strategy only involves children with underlying conditions, elderly people aged 60 years or more and health-care professionals. New vaccines such as the cold-adapted

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intranasal influenza vaccines will promote discussion concerning extension of the eligible groups or a comprehensive intervention in the paediatric population. In general, influenza is not considered a dangerous disease for children in our country. Amantadine as an anti-viral therapy is as yet highly underprescribed in Germany and the role of the new neuraminidase inhibitors in the treatment and prophylaxis of children has yet to be defined. To answer all these questions, epidemiological data are crucial. To elucidate at least the tip of the iceberg, the present study investigated the descriptive epidemiology of paediatric influenza-positive hospitalizations.

METHODS

Patients

From July 1996 to June 2001, children 0–16 years of age admitted to one of the local paediatric hospitals, either the University Children's Hospital or the Municipal Hospital Kiel, and from whom naso-pharyngeal aspirates (NPA) were taken, were included in the study. Kiel is the capital of Schleswig-Holstein, the northernmost federal state of Germany, with a total population of 2·7 million in 1997, of whom 427 516 individuals (15·7%) were children under 16 years of age [4].

The inclusion criterion was any acute respiratory infection (ARI), regardless of the reason for hospital admission. For calculation of incidences, only community-acquired infections were taken into consideration. Nosocomial transmission was assumed when the symptoms appeared more than 48 h after admission and the primary cause of admission was not an ARI. The NPA samples and basic data were collected prospectively. The NPA was taken within 48 h of admission, if possible, and processed immediately or stored at 4 °C until the next working day. The final clinical diagnosis, which was used for allocation of cases into disease categories, was made by a combination of chest X-ray results and clinical judgement by the treating team. The diagnosis and further details were obtained retrospectively from the patient's case notes and the discharge letter by doctoral students and cross-checked by the first author.

Virological methods

The NPA was investigated by a nine-valent multiplex reverse transcriptase PCR (m-RT–PCR) assay as recently described [5, 6]. Briefly, before July 1997, nucleic acid preparation was done by phenol–chloroform extraction and ethanol precipitation. Thereafter, the Boehringer–Mannheim 'High Pure Viral Nucleic Acid Kit' was used (Boehringer–Mannheim, Germany). The m-RT–PCR involved the reverse transcription of the RNA from RNA organisms (influenza A virus, influenza B virus, RSV, parainfluenza virus types 1 and 3, enterovirus) followed by a PCR amplification of the corresponding cDNA and of the DNA of adenovirus, *Mycoplasma pneumoniae* and *Chlamydia pneumoniae*, respectively. Primers were chosen from previously published highly conserved target sequences. For influenza A and B amplification primers with binding sites within the non-structural protein gene were chosen [7]. PCR products were analysed on 2% agarose gels and specified with the 'PCR-ELISA-Dig Detection System' from Roche Diagnostics GmbH, Germany. The validity of the m-RT–PCR was tested by comparison with immuno-fluorescence and cell-culture on MDCK (+trypsin), A549 (+trypsin), HEL and primary monkey kidney cell lines in cooperation with the Department of Virology, University of Rotterdam (unpublished observations) on separate sample collections. The values of the kappa statistic were 93·1% for influenza A, 88·2% for influenza B and 92·3% for RSV [8]. The rapid influenza A-EIA (Directigen™ Flu A, Becton Dickinson, Sparks, MD, USA) and RSV-EIA (Directigen™, Becton Dickinson) kits were used additionally to look for diagnostic escape mutants.

Definition of the sampling frame and calculation of the denominator

For the general description of the influenza-associated hospitalizations, all cases admitted to both hospitals, the University Children's Hospital as well as the Municipal Hospital's Department of Paediatrics, were reported. For population-based incidence calculations, only those cases from the denominator area 'Kiel' were included in the analysis. Therefore, the recruitment areas of both hospitals must be known. By plotting the cases according to origin (postal codes) and the locations of the 11 paediatric hospitals of Schleswig-Holstein, the areas of overlap could be recognized. Some postal codes are shared by nearby areas not belonging to the municipal area of Kiel (Kronshagen and Ottendorf), but situated as in a conclave of the municipal area of Kiel. They were included in the denominator since patients from these

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areas would also have been admitted to the two hospitals mentioned. The area of no interference from other hospitals is termed the denominator area 'Kiel', including Kiel itself, Kronshagen and Ottendorf. To avoid the risk of misclassification, the denominator area 'Kiel' was estimated very conservatively. The population data published by the Ministry for Labour, Health and Social Affairs of Schleswig-Holstein for 1997 were used [4]. Since the birth rate was reasonably constant over the years, the figures for 1997 were extrapolated to the total time span of this study. The birth cohort of 'Kiel' was 2830, with a fraction of prematures with a gestational age under 32 weeks of 1·34 and 6·77% for 32–36 weeks gestational age [9]. The crude numbers of the nominators of the incidence rates were corrected by the age-specific case ascertainment rate because the ascertainment of cases was incomplete and age-dependent. The case ascertainment rate in this context was the fraction of children admitted to one of the two hospitals with an ARI, in whom a NPA was sent for PCR testing.

For comparison of different influenza epidemics, grading according to 'epidemiological years' was undertaken. An epidemiological year is the time span from July onwards until the end of June the following year, placing in general the influenza season in the middle.

Since RSV is the major viral ARI pathogen in children and data for Germany have been recently published [10, 11], data for RSV are presented parallel to the influenza data as a scale and to compare the incidence of both groups of viruses directly. A further reason was that RSV in particular competes with influenza viruses for susceptible 'vector' children to spread the virus and to enhance the epidemic [2, 12–14].

The data were stored and processed in a computerized database (Microsoft Access, Microsoft, USA). SPSS version 10 was used for statistical analysis.

RESULTS

Ascertainment

In the study period from July 1996 to June 2001, a total of five winter seasons with a total of 3469 children hospitalized with ARI were observed. In 2108 cases (60·5%), NPA was tested by m-RT–PCR. Of all ARI patients, 122 (3·5%) were diagnosed with a community-acquired infection due to influenza A, 14 (0·4%) for influenza B and 325 (9·4%) for RSV (Table 1). Nosocomial infections were diagnosed: influenza A (10), influenza B (2) and RSV (24). In most instances only community-acquired infections are shown in detail, since nosocomial infections do occur unexpectedly. For detailed analysis, only the data of patients from 1996 to 2000 were used as the most recent epidemiological year has not yet been evaluated in detail. The case ascertainment rate was 71·0, 57·3 and 53·7% for children <1 year, >1 to 2 years and >2 years of age, respectively.

Table 1. *Numbers of hospitalizations due to community-acquired and nosocomial infections in Kiel, July 1996 to June 2001*

Epidemiological year	Number of community-acquired (nosocomial) cases		
	Influenza A	Influenza B	RSV
1996/7	11 (0)	10 (1)	51 (4)
1997/8	30 (2)	0 (0)	34 (7)
1998/9	29 (4)	4 (1)	47 (1)
1999/00	33 (3)	0 (0)	64 (2)
2000/1	19 (1)	0 (0)	129 (10)
Total	122 (10)	14 (2)	325 (14)

Table 2. *Age distribution of hospitalizations due to community-acquired respiratory infections, Kiel, July 1996 to June 2000*

Age group (years)	Influenza A *n* (%)	Influenza B *n* (%)	RSV *n* (%)
0–1	25 (24·5)	4 (28·6)	140 (71·4)
>1–2	24 (23·5)	2 (14·3)	29 (14·8)
>2–5	34 (33·3)	2 (14·3)	23 (11·7)
>5–16	19 (16·6)	6 (42·9)	4 (2·0)
Total	102 (100·0)	14 (100·0)	196 (100·0)

Age and gender distribution

The age distribution was different for the three infections (Table 2). For RSV, 71·4% of hospitalizations occurred in the first year of life and declined sharply thereafter with only 2% of cases older than 5 years. For influenza A, the fraction was 23·5–33·3% per age group under 5 years and declined thereafter. For influenza B the highest percentage was in children older than 5 years. This is also underlined by the median age of 752 days (mean = 1102) for influenza A, 966 days (mean = 1591) for influenza B and 168 days (mean = 332) for RSV. The female to male ratio was 1 to 1·29

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Table 3. *Underlying conditions in hospitalized children with community-acquired respiratory infections*

	Number of cases with		
Condition	Influenza A	Influenza B	RSV
Asthma	5	0	5
Pulmonary others	0	2	8 (BPD 5)*
Cardiac	6	2	10
Neurological	2	2	3
Malformations	2	—	3
Metabolic	3	—	1
With condition total	18 (17·6%)	6 (42·9%)	30 (15·3%)
Without condition total	84 (82·4%)	8 (57·1%)	166 (84·7%)

* BPD, broncho-pulmonary dysplasia.

Table 4. *Population-based incidences of hospitalizations according to gestational age in children 0–16 years of age*

		Influenza A			Influenza B			RSV		
Gestational age (weeks)	Expected (%)	*n* (%)	i*	RR†	*n* (%)	i	RR	*n* (%)	i	RR
24–31	1·34	2 (2·0)	87	1·6	0 (0)	0	—	8 (4·1)	348	3·4
32–36	6·77	16 (15·7)	138	2·6	1 (7·1)	34	4·3	28 (14·3)	241	2·4
⩾37	91·79	85 (83·3)	54	ref.	13 (92·9)	8	ref.	160 (81·6)	102	ref.
Total	100·00	102 (100·0)	59	—	14 (100·0)	8	—	196 (100·0)	114	—

* i, incidence per 100 000 average over 4 years (1996–2000).
† RR, relative risk.

in influenza A, 1 to 1·29 in influenza B and 1 to 1·28 in RSV.

Disease categories

Of the 102 influenza A patients, 52 (51%) had ''flu' or an upper respiratory tract infection (URI), 1 had laryngo-trachaeo-bronchitis (LTB), 12 (12%) had bronchitis, 11 (11%) had wheezing bronchitis and 26 (25%) had pneumonia. Of the 14 influenza B infections, 2 (14%) had an URI or 'flu, 1 had LTB, 4 (29%) had bronchitis, 2 (14%) had wheezing bronchitis and 5 (36%) had pneumonia. For RSV 14 had an URI (7%), none had LTB, 20 (10%) had bronchitis, 71 (36%) had wheezing bronchitis and 91 (46%) had pneumonia. Since this study is hospital-based, there is a clear preponderance of lower respiratory tract infections. The proportion of lower respiratory tract infections in influenza A (48%) and B (79%) was less than in RSV (93%). Influenza A infection was complicated by a concomitant otitis media in 26 cases (25%), by severe anaemia in 1 and syncope in 1 case. No otitis media was diagnosed in influenza B cases. One adolescent with influenza B had myositis of the calf muscles. RSV was complicated by concomitant otitis media in 25 (13%) cases.

Underlying condition and gestational age

An underlying condition was present most frequently in influenza B cases (42·9%) (Table 3). Asthma was twice as common in influenza A (4·9%) as in RSV (2·6%) cases. Cardiac conditions were of similar prevalence – 5·9% in influenza and 5·1% in RSV. Nosocomial transmissions were more common in cases with than without an underlying condition. In influenza A 50% (5 of 10), in influenza B 50% (1 of 2) and in RSV 64% (9 of 14) of patients with a nosocomial infection had an underlying condition in contrast to 17·6, 42·9 and 15·3% in community-acquired infections, respectively. With regard to gestational age, the proportions between influenza A and RSV were similar (see absolute numbers and percentages in Table 4). In influenza B, only one case was born

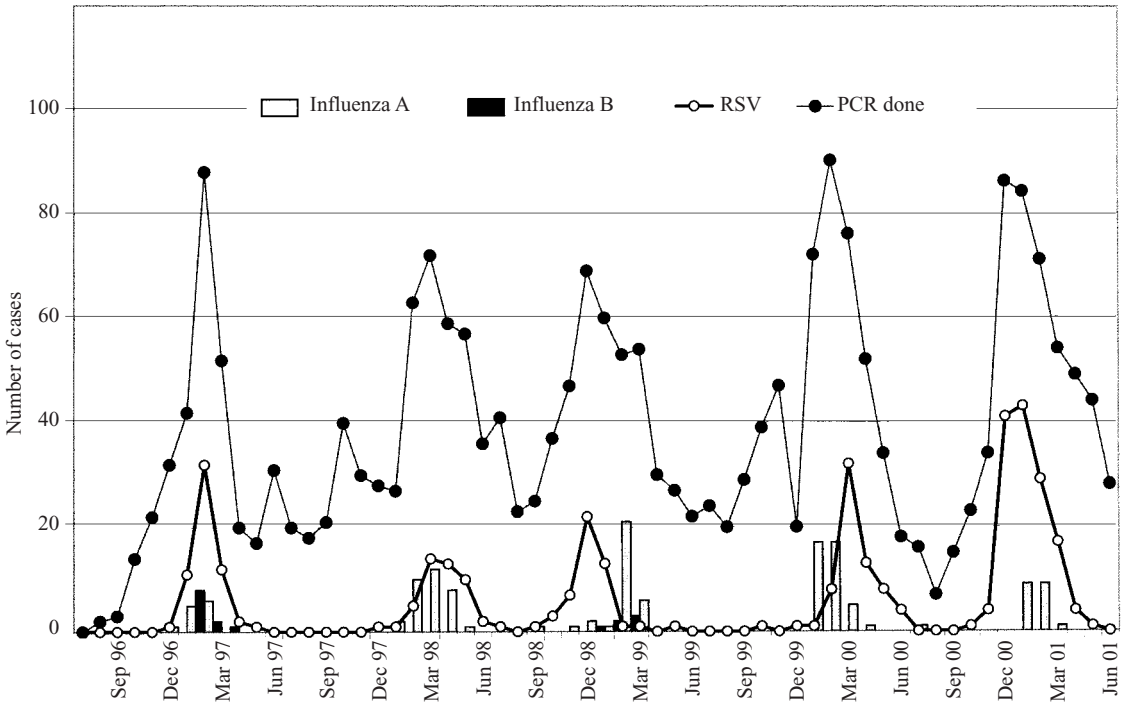

Fig. 1. Numbers of hospitalizations associated with influenza A, B and RSV in children 0–16 years of age from July 1996 to June 2001.

prematurely. It has to be remembered that influenza B cases were nevertheless considerably older than patients of the other groups, especially the RSV group.

Seasonality

Figure 1 and Table 1 show the total number of hospitalized cases for the three pathogens over time. After 1996/7 the number of RSV-positive admissions dropped and thereafter increased continuously. In all seasons RSV was of higher impact than influenza. Influenza B only occurred in the years 1996/7 and 1998/9. Considering influenza A, varying patterns in comparison to RSV occurred. In the years 1996/7 and 2000/1 with very pronounced RSV epidemics, the incidence of influenza A was low. In the year 1998/9 it appears that the RSV season was terminated by the upcoming influenza A season and in the year 1999/00 vice versa. Only in the year 1997/8 were the two viruses of similar importance.

The RSV season showed considerable variation in time of onset and end; by contrast the influenza A season started regularly between weeks 50 and 4 of a calendar year and lasted 3–4 months. Again these data refer to the total sample irrespective of the place of residence.

Population-based incidences

To calculate population-based incidences, the crude data per age group and the age group-specific case ascertainment rate were considered (Table 5). The age group >5–16 years with the lowest incidence was taken as the reference for each category, respectively. As the age distribution already indicated, the population-based incidence in children under 5 years was greatest in RSV with a relative risk (RR) of 29–390 in comparison to children over 5 years of age. In influenza A it was much lower (4·6–7·3). Pooling children under 2 years of age with influenza A, the RR in comparison to >5- to 16-year-old children would be 7. For influenza B the RR is even lower taking the small crude numbers into consideration.

Risk factors

Asthma, as the single most frequent underlying disease entity in influenza A and RSV, carried a RR of 4·1 (95% CI 1·67, 9·98) and 2·1 (95% CI 0·88, 5·15), respectively. Given the prevalence of cardiac conditions of 0·6% in the paediatric population, the RR for hospitalization was 9·8 (95% CI 4·33, 23·15) for influenza A and 8·5 (95% CI 4·55, 15·87) for RSV. The population-based incidence of influenza A was doubled

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Table 5. *Population-based cumulative incidence* (per 100 000), 4 year average, 'Kiel', July 1996 to June 2001*

Age group (years)	Case ascertainment rate (%)	Influenza A		Influenza B†		RSV	
		n	(RR)	*n*	(RR)	*n*	(RR)
0–1	71·0	149	(6·8)	49	(5·4)	1563	(390)
>1–2	57·3	161	(7·3)	31	(3·4)	358	(90)
>2–5	53·7	101	(4·6)	24	(2·7)	115	(29)
>5–16	53·7	22	(ref.)	9	(ref.)	4	(ref.)
Total 0–16	60·5	53		16		165	

* Corrected by age-group specific case ascertainment rate.
† Only present in two epidemiologic years (1996/7 and 1998/9).

in children with a gestational age under 37 weeks, but there was no dose–effect relationship between gestational age and the chance of an influenza-positive hospitalization as observed in RSV (Table 4).

DISCUSSION

According to our knowledge, the study presented here is the most extensive population-based analysis of the incidence of influenza-associated hospitalizations in children in Germany to date. Also, so far, no data on the population-based incidence of influenza in outpatients or in the population exist.

The ascertainment rate was higher in the younger patients. This is in line with previous observations [6, 11]. Surveillance by m-RT–PCR was started in the winter 1995/6 and after 1 year a case ascertainment rate of at least 50% was reached. Since then, it was between 55 and 66%, i.e. a variation of 11%. It has to be mentioned that study or research nurses were not available and the collection of NPAs was dependent upon ward team compliance. It also was higher in the University Children's Hospital, the home institution. Since the age group-specific case ascertainment rates were known, the crude data could be corrected accordingly for incidence calculations.

The m-RT–PCR is an established tool in our department and was validated as mentioned. As the three viruses can mutate either in primer or probe binding sites, a second, simple and non-genome-based method, i.e. an EIA for influenza A and RSV, was used. During the 5-year period, a second detection probe for RSV had to be added as from 1998/9 onwards a RSV strain occurred with a point mutation in the centre of the probe binding site [11]. Taking all these efforts together, we are sufficiently sure of the accuracy and the precision of the virological methods and insufficient diagnostic work-up is an unlikely explanation for differences in the cumulative incidences.

The age and gender proportions in our study are as described by others [12, 15–17]. In contrast to RSV, influenza A and B more frequently involve older children [16]. In an earlier publication, we called this the 'subtype phenomenon' [6]. This means a virus attacks older age groups of children when it can form more subtypes than another virus. Influenza B could appear as a contradiction, but one has to remember that it is by far less potent in causing severe disease leading to hospitalization. It attacks more children with an underlying condition [18], which accumulate with age [19]. Therefore influenza B is of particular importance in children older than 5 years [16] as it was in our study.

It is widely accepted that influenza A and B have a far wider range of disease entities than RSV, which is mainly confined to the airways, in particular the lower airways. Influenza A and B can imitate bacterial septicaemia, can cause encephalitis, myositis and Reye's syndrome [20, 21]. Only one case of myositis of the calf muscles was present in our sample. As the surveillance of our unit mainly focuses on ARI conditions, some systemic conditions could have been missed. Since they occur rarely without at least an URI or ''flu', this is, however, not very likely. The lower proportion of lower respiratory tract infection in influenza A and B in contrast to RSV is a frequent observation [21, 22].

There is considerable discussion in the literature about the interference of influenza and RSV in the winter epidemics [2, 12–14, 23]. The discussion relates to which virus is blocking the other, whether two viruses can co-circulate in a simultaneous fashion or which one is dominant. The time curve in Figure 1 of

Table 6. *International comparison of cumulative incidences of influenza-associated hospitalizations by age group*

Place (ref.)	Time	Incidence* 0–5 years	Incidence* >5 to 16/17 years	Relative risk†
Houston [27]	1985–1990	427	5	85
California [15]	1967–1973	120	40	3·0
California [12]	1993–1997	136	19	7·2
Seattle [12]	1992–1997	90	16	5·6
Kiel [reported study]	1996–2001	123	22	5·6
California [15]‡	1967–1972	470	210	2·2
Tennessee§ [28]	1973–1993	382	40	9·6

* Per 100 000.
† >5–16/17 years as reference.
‡ All with underlying conditions (any).
§ All with underlying cardiac conditions.

our study gives an example. In our opinion it is more important to focus on the enhancing mechanisms of an ARI epidemic. School age and preschool children are the major amplifiers of an epidemic of ARI organisms in general and influenza in particular (turbo-mechanism). Glezen called children 'the fire of the epidemic' [2]. This was finally proven by the study of Reichert et al. [3], at least for Japan. How much influenza impacted on excess mortality in the United States is not so striking. Nicholson [13] could show for England and Wales that RSV seems to be more important (1·5–1·8 times) than influenza. Different mechanisms for the interaction between influenza and RSV, and most likely other ARI pathogens [23], are possible: the pool of susceptible children to enhance the epidemic is limited, or the pathogens dominate on a first come first served basis, or block at the cellular level by not allowing infection of a cell of the airway epithelium once an infection with another ARI virus has already occurred, or just the total number of viruses and strains circulating at the same time.

Brandenburg et al. [24] and our group [11] mentioned a so far 'unknown factor' contributing to the severity of RSV epidemics in different places. The turbo-mechanism and the competition for it could be one decisive clue. This underlines the need for pathogen-specific surveillance instead of syndromic surveillance to determine the attributable fractions for different pathogens within one given ARI epidemic.

A more or less stable onset and end of the yearly influenza A epidemic has been reported in other areas [16, 25, 26]. All 5 years under observation in this study occurred under conditions of antigenic drift only. Why the seasonality of influenza A is so much more constant in terms of onset than that of RSV is not yet clear. Climatic factors may only be part of the explanation. Influenza B shows 2–4 years inter-epidemic intervals as was shown in our study [16, 21].

Taking more recent data from the United States, our incidence figures are similar to those of Izurieta et al. [12] (Table 6). Why the data published by Glezen [27] earlier were so much higher, is more likely explained by changes in the health care system with more recent stricter admission criteria. If surveillance is only syndromic and not supplemented sufficiently by virological diagnostics, the incidence can be overestimated (e.g. as in [15, 26]). The similarities of our data with recent US data [12] suggest that the epidemiology of excess mortality due to influenza in Germany should be more similar to the conditions in the United States than in Japan [3]. One likely explanation would be the family structure, which in Germany is supposedly more similar to the United States than to Japan.

Pulmonary (especially asthmatic) and cardiac underlying conditions are the known major risk factors for influenza-related hospitalizations [19]. For cardiac diseases the risk ratio is at least 2–3 as shown by Neuzil et al. [28]. Glezen [19], as in our study, showed cardiac conditions in children are even of higher impact than pulmonary conditions. Within the latter asthma is a major risk factor [29] as confirmed by our study. For influenza B, a less potent virus than influenza A in terms of number of cases with severe disease leading to hospital admission, the underlying condition is the major risk factor increasing the probability of an influenza B-positive hospitalization [18]. The fraction with underlying conditions was also highest (43 %) in

influenza B in our study. Nosocomial infections are more likely to occur in patients with underlying conditions as their time in hospital is longer [30].

In influenza A, low gestational age doubles the risk of hospitalization, but gestational age is not in a clear dose–effect relationship to the incidence as described for RSV [10]. Broncho-pulmonary dysplasia was a clear risk factor (RR 17·4) for children under 2 years of age born before 32 weeks gestational age [10].

The population-based incidence of influenza-positive hospitalizations is the same in our study as reported recently from the United States. Asthma and cardiac diseases are special risk factors for hospital admission for influenza infections. The overall importance for hospital care of influenza infections in contrast to RSV is about one third taking into consideration that the spectrum of disease in influenza is broader than in RSV infections and that influenza-associated hospitalizations extend to older age groups. Targeting children with underlying conditions for vaccination against influenza in the German immunization programme is appropriate as long as no recommendation exists to vaccinate the general paediatric population.

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