Epidemiol. Infect. (2017), **145**, 2683–2693. © Cambridge University Press 2017
doi:10.1017/S0950268817001777

A national register-based study of paediatric varicella hospitalizations in Denmark 2010–2016

I. G. HELMUTH[1,2]*, A. POULSEN[1] AND K. MØLBAK[2]

[1] *Department of Paediatrics and Adolescent Medicine, Rigshospitalet, Copenhagen, Denmark*
[2] *Department of Infectious Disease Epidemiology, Statens Serum Institut, Copenhagen, Denmark*

Received 20 January 2017; Final revision 1 June 2017; Accepted 17 July 2017; first published online 14 August 2017

SUMMARY

Varicella, usually a mild disease of childhood, can also cause complications and hospitalization. Universal varicella immunization is implemented in several countries worldwide, but not in Denmark. Taking advantage of unique national registers, we aimed to estimate the incidence of paediatric varicella hospitalizations and assess determinants for hospitalization. For this purpose, we designed a nationwide, retrospective register study of paediatric varicella hospitalizations and applied a case–cohort design and logistic regression analysis comparing hospitalized varicella patients to a sample of the entire paediatric population in Denmark. Varicella patients were identified in The Danish National Patient Register and referents were randomly selected from the Danish Civil Registration System. The incidence of paediatric varicella admissions was 11/100 000 children 0–18 years of age/year. Of admitted children 67·1% had complications and 30·0% had underlying disease. All categories of underlying disease significantly increased the odds of hospitalization as well as male gender and not having been born in Denmark. In conclusion, we found a considerable burden of paediatric varicella disease in Danish hospitals, of similar magnitude as in other European countries comparable to Denmark. With this study we have provided epidemiological data needed for considering implementation of varicella vaccine in Denmark.

Key words: Paediatric varicella hospitalizations, varicella complications, varicella epidemiology, varicella zoster virus.

INTRODUCTION

Varicella, caused by varicella zoster virus (VZV), is an acute febrile illness characterized by a universal vesicular rash. Varicella is usually mild, but can also result in complications and hospitalization. In European countries without universal vaccination, varicella affects about 90% of children before the age of 10 years [1–3]. After primary infection, the virus lies dormant in nerve ganglia and can later reactivate to cause herpes zoster – a painful rash usually confined within a dermatome [1].

Varicella is preventable by a live-attenuated vaccine available as a monovalent vaccine or in combination with measles–mumps and rubella. Varicella vaccination has shown to be both safe and effective in preventing varicella, but less so in preventing herpes zoster [1, 2, 4]. WHO recommends that childhood varicella immunization is considered in countries where the disease has a high impact on public health and where high vaccination coverage (85–90%) can

* Author for correspondence: I. G. Helmuth, Department of Infectious Disease Epidemiology, Statens Serum Institut, Artillerivej 5, 2300 Copenhagen S, Denmark.
(Email: IDGK@ssi.dk)

be achieved [5]. Countries that have implemented universal varicella immunization including the USA, Germany and Australia have experienced a marked decrease in disease burden [6–11]. Rates of hospitalization, complications and severity of varicella has been described for several European countries [12–15], but only few have adopted the vaccine in national immunization schemes [15, 16]. Results of epidemiological studies on varicella vary across Europe due differences in study design, urbanization and patterns of childcare [15, 16]. Hence, when deciding on national strategies for childhood varicella vaccination, national studies on disease epidemiology are essential. In Denmark, varicella vaccination is not a part of the national childhood immunization scheme, varicella is not notifiable and the burden of disease has not been assessed on a national level.

The primary aim of this study was to estimate the incidence of paediatric varicella hospitalizations in Denmark and describe characteristics of children hospitalized with varicella. The secondary aim was to assess determinants for paediatric varicella hospitalization. To meet this objective, we took advantage of unique national registries allowing for unbiased estimates and an analytic epidemiological approach.

METHODS

The study was designed as a retrospective, nationwide population-based register study. We applied a case–cohort design and logistic regression analysis to assess determinants for hospitalization with varicella comparing hospitalized paediatric varicella patients to a randomly selected reference group representing the entire paediatric population in Denmark.

Denmark has a population of 5·6 million. Healthcare is tax funded and free of charge for all residents. The five regions in Denmark are responsible for providing healthcare. At birth, all residents are assigned a unique Civil Registry number (the CRS-number) used to register the utilization of healthcare services. The CRS-number allows for linkage between Danish registries at individual level [17, 18]. Patients that are not Danish citizens at time of hospitalization are assigned a temporary unique CRS-number.

The Danish National Patient Register (DNPR) contains information on all in- and outpatient contacts for all hospitals in Denmark. It includes the start and end date of in- and outpatient contacts and discharge diagnoses. Diagnoses are coded according to the ICD10 (International Classification of Diseases 10th revision). For diagnoses, it is possible to register one primary diagnosis, while there is no upper limit to the number of secondary diagnoses [18, 19]. The DNPR does not contain information from general practitioners. However, in 2014 one of the five Danish regions, the Capital Region, introduced a new hospital-based system for primary care patients seen out-of-hours, and therefore these are registered in DNPR as outpatient contacts from January 2014.

We included all hospital contacts of children <18 years of age in DNPR with a primary or secondary diagnosis of varicella (ICD10 codes B01-B019 and P358A) in any diagnostic position in a period of 6 years from 1 January 2010 to 31 December 2015. We included patients with a temporary CRS-number and patients from Greenland admitted in Danish hospitals as they contributed to the overall burden and could represent refugees or migrants.

We excluded patients with a start date before 2010, outpatient contacts lasting >2 months because a disease onset could not be determined and patients registered in 2014–2015 at departments serving paediatric primary care patients seen out-of-hours in the Capital Region.

We grouped patients in two groups: (1) admitted patients were defined as patients coded as inpatients with admissions lasting $\geqslant$1 day and (2) outpatients defined as patients coded as inpatients for <1 day or outpatients. Collectively we will refer to these two groups as 'hospitalizations'.

For inpatients with several discharge diagnoses of varicella within a short time period, we created courses of admissions. This was done because transfer between hospitals or between departments in one hospital in many cases was coded as individual admissions in DNPR, and admission time could therefore be incorrectly estimated unless we reconstructed the full course of admission. Several admissions for the same patients were defined as one course of admission if the timespan between discharge and a new admission was <1 day. Length of admission was counted as total days between the first admission and the last discharge.

We defined the date of varicella as the first day of admission or date of first outpatient visit. Only first course of admission or outpatient visit was analysed.

To assess complications to varicella, we extracted all other primary or secondary discharge diagnoses in any diagnostic position given with a varicella code in any diagnostic position. ICD10 codes used

https://doi.org/10.1017/S0950268817001777 Published online by Cambridge University Press

to define complications to varicella are available in Supplementary material and were completed in cooperation with a specialist in paediatric infectious diseases.

To assess underlying medical conditions, we extracted all primary or secondary discharge diagnoses in any diagnostic position in DNPR for included patients up to 5 years before to 3 weeks after the varicella date. ICD10 codes defined as an underlying condition are available in Supplementary material and were completed in cooperation with a specialist in paediatric infectious disease. For conditions that could be both a complication and an underlying disease, a time restriction for the underlying disease was added.

The Danish Civil Registration System (CRS) contains individual-level information on the entire population of Denmark including vital and migration status [17]. We obtained country of birth, province of residence at date of varicella and vital status for cases up to 90 days after varicella date.

Statistical analysis

We performed a descriptive analysis of the paediatric varicella hospitalizations. We described continuous variables in medians, IQR and maximum values since all continuous variables were skewed to the right. We calculated incidence using the census of 2013 as the denominator (1·190·301 children 0–18 years of age). Categorical data were compared using a χ^2 test.

We used a case–cohort design and performed a logistic regression analysis to assess determinants for a hospitalization with varicella comparing all the identified varicella patients to a sample of the entire paediatric population of Denmark (i.e. referents). In this approach, cases were allowed to be sampled for the reference group. We randomly selected 10 referents for each case from CRS matched for year of birth to ensure equal distribution of age groups between cases and referents. We excluded referents if they were born after the date of varicella for the corresponding case or if they were born abroad and had not entered Denmark at date of varicella for the corresponding case. This was done to ensure that cases and referents would have equal time at risk when assessing underlying diseases. If a case had no referents after running the exclusion procedures, we randomly re-sampled new referents so that each case had at least two referents. Underlying diseases were assessed for referents as for cases up to 5 years before and 3 weeks after the date of varicella for the corresponding case.

For the logistic regression model, we evaluated the following independent variables by univariable analysis while controlling for the matching factors (year of birth categorized in nine categories and date of varicella for the case categorized in years): gender, underlying disease (categorized according to Supplementary material) and country of birth (dichotomized into Danish or non-Danish origin due to high number of unknown country of birth among the cases). Country of birth was categorized as non-Danish if it was unknown. Variables associated with being a case at a significance level of 10% were considered for the multivariable model and subsequently eliminated if they did not contribute at a significance level of 5%. The final model was controlled for region of residence and the matching factors.

To evaluate relevant interactions in the logistic regression model, we also performed the analysis stratified on the following age groups: 0–1 years of age, 2–3 years of age and >4 years of age (data not shown). In the stratified analysis, all categories of underlying disease were independently associated with the outcome (except for a history of prematurity in the age group >4 years of age). The effect size differed from the overall model for some categories of underlying disease, but overall findings remained consistent but with wider confidence limits. At the chosen level of categorization of diagnosis, a formal test for interaction was impossible to conduct due to sparse data.

To assess determinants for admission $\geqslant 1$ day, we also conducted a logistic regression analysis only among cases. We assessed the following independent variables by univariable analysis sex, age (dichotomized in age > or <1 year), country of birth, underlying disease and complications to varicella. The final model was controlled for region and year of hospitalization.

Analyses were performed using STATA (version 12.1, STATA, College Station, Texas, USA).

Ethical considerations

The study was notified to the Danish data protection agency under the record number 2008-54-0474. Danish legislation does not require ethical board approval or informed consent from study participants in register studies [20].

https://doi.org/10.1017/S0950268817001777 Published online by Cambridge University Press

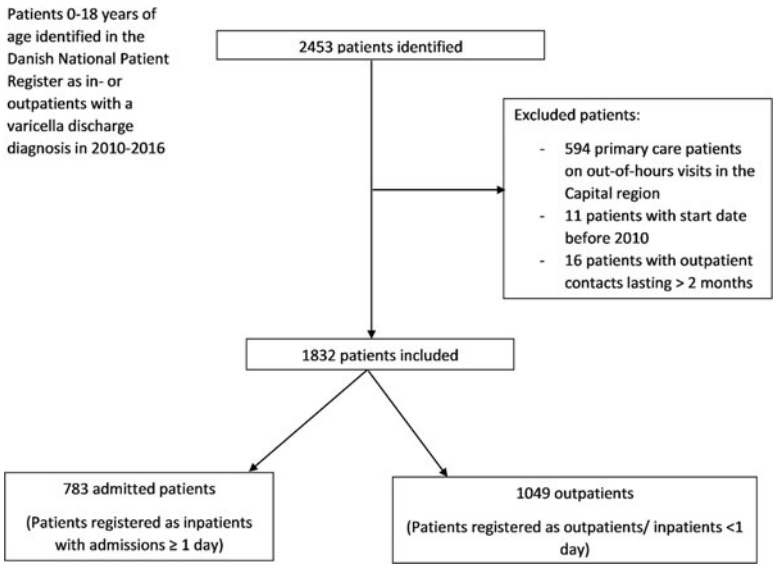

Fig. 1. Flowchart of in- and exclusion of patients hospitalized with varicella in Denmark 2010–2016.

RESULTS

Descriptive epidemiology

In DNPR, we identified 2857 hospitalizations, 1592 inpatient contacts and 1265 outpatient contacts. The total number of unique patients was 2453. Of those 621 were excluded; 594 patients were primary care patients on out-of-hours visits in the Capital Region, 11 patients were registered with a start date before 2010, 16 patients had outpatient contacts lasting >2 months. A total of 1832 patients were included; 783 patients registered as inpatients with admission $\geqslant 1$ day and 1049 as outpatients/inpatients <1 day (collectively referred to as outpatients) (Fig. 1). A total of 41 patients (2·2%) were registered with a temporary CRS-number, and four patients were registered as citizens of Greenland.

The hospitalizations displayed a seasonal variation with the highest number of contacts in late winter and early spring and a nadir in August and September (Fig. 2).

General characteristics of patients hospitalized with varicella are presented in Table 1 and the frequency of registered complications for all patients and admitted patients in Table 2. Most patients were previously healthy children between 1 and 4 years of age. The median age was 2 years (IQR 1–3). Underlying disease was identified in 22·1% of short contact patients and 30·0% of admitted patients ($P < 0{\cdot}001$). The frequency of complications was 31·1% for outpatients and 67·1% for admitted patients ($P < 0{\cdot}001$). Of children with underlying disease, 47·3% were registered with

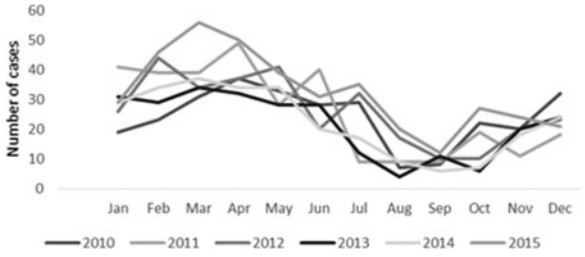

Fig. 2. Seasonal variation of paediatric varicella hospitalizations in Denmark 2010–2016.

complications *vs.* 46·2% of patients without underlying disease ($P = 0{\cdot}66$). The most common complications were from the central nervous system including febrile seizures, followed by complications of the skin and lower airways (17·5% and 11·0% of admitted patients, respectively). The median age of children with complications of the central nervous system excluding febrile seizures was 4 years (IQR 2–8, max 15), while the median age of children with complications of skin and soft tissue was 2 years (IQR 1–3, max 13).

Two patients were registered with congenital varicella (ICD10 code P358A).

Of the 1832 patients, 94·1% were born in Denmark. For the remaining 109 patients, the country of birth could be determined for 67 patients; patients with a non-western region of birth (Greenland, The Middle east and North Africa including Pakistan, Afghanistan and Turkey, Southeast Asia, Latin America and Africa) were older (median age 4

https://doi.org/10.1017/S0950268817001777 Published online by Cambridge University Press

Table 1. *General characteristics of paediatric patients hospitalized with varicella in Denmark 2010–2016 identified in the Danish National Patient Register*

	All patients	Outpatients[a]	Admissions[b]
No. of patients, *N* (%)	1832	1049 (57·3)	783 (43·7)
Females *N* (%)	832 (45·4)	483 (46·0)	349 (45·6)
Age groups *N* (%)			
0 years	399 (21·8)	205 (19·5)	194 (24·8)
1–4 years	1155 (63·1)	675 (64·4)	480 (61·3)
5–18 years	278 (15·2)	169 (16·1)	109 (13·9)
Patients with underlying disease[c], *N* (%)	467 (25·5)	232 (22·0)	235 (30·0)
Patients with immunosuppressive condition[d], *N* (%)	105 (5·7)	35 (3·3)	70 (8·9)
Patients with complications[e], *N* (%)	851 (46·5)	326 (31·1)	525 (67·1)
Length of admission (median (IQR) max)	–	–	2 (1,4) 74

[a] Defined as patients registered as outpatients or inpatients for <1 day.
[b] Defined as patients registered as inpatients for ⩾1 day.
[c] Defined as being registered with an ICD10 diagnosis compatible with underlying medical condition in the Danish National Patient Register up to 5 years before and 3 weeks after the varicella diagnosis.
[d] Defined as being registered with cancer disease, auto immune disease or other immunosuppressive conditions in the Danish National Patient Register up to 5 years before and 3 weeks after the varicella diagnosis.
[e] Defined as being registered with an ICD10 diagnosis compatible with complications of varicella in the Danish National Patient Register at time of hospitalization for varicella.

years, IQR (2–6)) than patients with a western region (Denmark and Europe) of birth (median age 2 years, IQR (1–3)).

The overall incidence of hospitalization with varicella was 26/100 000 children 0–18 years of age/year. The incidence of children with outpatient contacts was 15/100 000 children 0–18 years of age/year and the incidence of admissions lasting ⩾1 day was 11/100 000 children 0–18 years of age/year (Table 3). The highest incidence of hospitalization was in the Capital Region of Denmark. The highest age-specific incidence was in children <2 years of age (Fig. 3).

We identified one death; a 7-year-old boy born in Asia and previously registered in DNPR with iridocyclitis on numerous occasions indicating autoimmune disease. He was registered as hospitalized with encephalitis and pneumonia due to varicella as well as endocarditis. He died after 14 days of admission. The mortality rate was 0·014/100 000 children 0–18 years of age/year.

Logistic regression analysis

After excluding 1138 children randomly selected as referents from CRS, the total number of referents used for analysis was 17 182 children including 35 cases (0·2%). A total of 1731 (10·1%) referents were registered with underlying disease using the same criteria as for cases.

Table 4 presents results of uni- and multivariable analysis of determinants for any kind of hospital contact with varicella. All categories of underlying medical conditions increased the odds of hospitalization, but the greatest odds were found in patients with cancer and autoimmune disease with odds ratios of 17·0 (95% CI 8·6–33·3) and 12·0 (95% CI 7·5–19·3), respectively. Furthermore, not being born in Denmark and male sex raised the odds of hospitalization.

Table 5 presents results of uni- and multivariable analysis with admission ⩾1 day as the outcome among the 1832 patients hospitalized with varicella. Cancer disease, autoimmune disease, age <1 year and complications to varicella raised the odds of being admitted ⩾1 day.

DISCUSSION

The incidence of paediatric varicella admissions ⩾1 day was 11/100 000 children 0–18 years of age. This is lower than reported from other European countries including France, Belgium and Spain with incidences of admissions of 28–30/100 000 children 0–16 years of age and 23/100 000 children 0–14 years of age, respectively [12, 21, 22], but in line with estimates from Germany, Italy and Sweden [13, 23, 24]. Due to vast differences in study design and healthcare systems, it is difficult to compare incidences and the epidemiology of varicella across European countries.

https://doi.org/10.1017/S0950268817001777 Published online by Cambridge University Press

Table 2. *Complications*[a] *in paediatric patients admitted with varicella in Denmark 2010–2016*

Organ system	All patients[b] *N* = 1832, *N* (%)	Admitted patients *N* = 783, *N* (%)
Any complication	851 (46·5)	525 (67·1)
Unspecified[c]	111 (6·1)	63 (8·0)
Central nervous system	227 (12·4)	137 (17·5)
Febrile seizure	147 (8·0)	76 (9·7)
Encephalitis/meningitis/ myelitis	53 (2·9)	43 (5·5)
Ataxia	10 (0·6)	10 (1·3)
Stroke/cerebral vasculitis	3 (0·2)	2 (0·3)
Skin	128 (7·0)	86 (11·0)
Infection of skin and soft tissue	104 (5·7)	74 (9·5)
Lower airways	120 (7·0)	85 (10·9)
Pneumonia	47 (2·6)	36 (4·6)
Dehydration	108 (5·9)	77 (9·8)
Upper airways	95 (5·2)	45 (5·8)
Gastrointestinal	49 (2·7)	30 (3·8)
Gastroenteritis	42 (2·3)	27 (3·5)
Appendicitis	3 (0·2)	2 (0·3)
Heart and circulation	28 (1·5)	24 (3·1)
Sepsis	17 (0·9)	17 (2·2)
Myocarditis/endocarditis	2 (0·1)	2 (0·3)
Muscular skeletal system	24 (1)	15 (2)
Septic arthritis/ osteomyelitis	5 (0·3)	5 (0·6)
Urinary and kidney	20 (1·1)	13 (1·7)
Urinary tract infection	14 (0·8)	8 (1·0)
Glomerulonephritis	6 (0·3)	5 (0·6)
Eyes	17 (0·9)	10 (1·3)

The table display number of children registered with ICD10 codes compatible with complications to varicella distributed on organ systems. Number of children with specific complications within an organ system are shown when found important. Patients can be registered with multiple complications and appear more than once.

[a] Defined as being registered with an ICD10 diagnosis compatible with complications of varicella in the Danish National Patient Registry at the time of hospitalization for varicella.

[b] All patients refers to all outpatients and admitted patients collectively.

[c] Defined as being registered with an ICD10 diagnosis of B019 (varicella with other complication) and no other ICD10 codes compatible with complications in the Danish National Patient Register at the time of hospitalization for varicella.

Although we took advantage of national registries, our study has several limitations, including the retrospective approach and the possible underestimation of the incidence of varicella hospitalizations that can occur because of error in ICD10 coding in clinical practice. The DNPR is generally considered of high quality, but it is possible that not all patients with varicella-related hospitalizations are coded with a varicella code. This could particularly be true when varicella complications are the main reason for hospitalization. In a previous prospective study of varicella hospitalizations in four paediatric departments [25], we found that the sensitivity of DNPR was 74% and applied, this could mean that the 'true' incidence of varicella admissions in Denmark is 15/100 000 children 0–18 years of age rather than 11/100 000. However, including children with temporary CRS number and four residents of Greenland may result in some overestimation. Overestimation is also a possibility if the positive predictive value of a varicella ICD10 code in DNPR is low, but we believe that the characteristic clinical features of varicella will lead to very few patients receiving a varicella discharge code if they are not ill from varicella.

The incidence of varicella in a country like Denmark is assumed to be approximately the size of a birth cohort [13] and applied to Denmark with a birth cohort of ≈60 000 children, the incidence of admissions due to varicella is 2/1000 cases of varicella (assuming that all cases happen in children <18 years of age). This is also in line with what has been found elsewhere in Europe [13, 24, 26].

A total of 67·1% of children admitted ⩾1 day with varicella were registered with additional ICD10 codes compatible with complications. Though this number is also subject to possible underestimation, our finding corresponds well with other European countries – reported complication rates in Germany and Belgium are 65–80% [12, 13]. The distribution of complications vary across studies with skin complications being the most common complications in some studies and neurological in others [15]. The differences are probably due to study design, definition of complications, ascertainment bias and the organization of healthcare systems. In Denmark, most minor complications to varicella like secondary skin infections will be handled by the family doctor and thus never be registered in DNPR. A limitation of the present study was that 8·0% of patients were registered with an ICD10 code of B018 for varicella with other complication, making it impossible to classify the complication within a specific organ system. We found skin complications in 11·0% of admitted children and neurological complications in 17·5%, although lower numbers than in other studies, the pattern of complications is similar [15]. Of importance, the frequency of complications was not higher in patients with

https://doi.org/10.1017/S0950268817001777 Published online by Cambridge University Press

Table 3. *Incidence of paediatric varicella hospitalizations*[a] *in the five regions of Denmark 2010–2016*

	Capital Region	Region Zealand	Region of Southern Denmark	Central region	North region	All regions
All hospital contacts (no. cases/annual incidence/100 000)	644 (30)	296 (28)	395 (25)	359 (21)	138 (19)	1832 (26)
Outpatients (no. cases/annual incidence/100 000)	426 (20)	157 (15)	198 (13)	205 (12)	63 (9)	1049 (15)
Admissions $\geqslant$1 day (no. cases/annual incidence/100 000)	218 (10)	139 (13)	197 (13)	154 (9)	75 (10)	783 (11)

[a] Hospitalization defined as all in- and outpatient contacts.

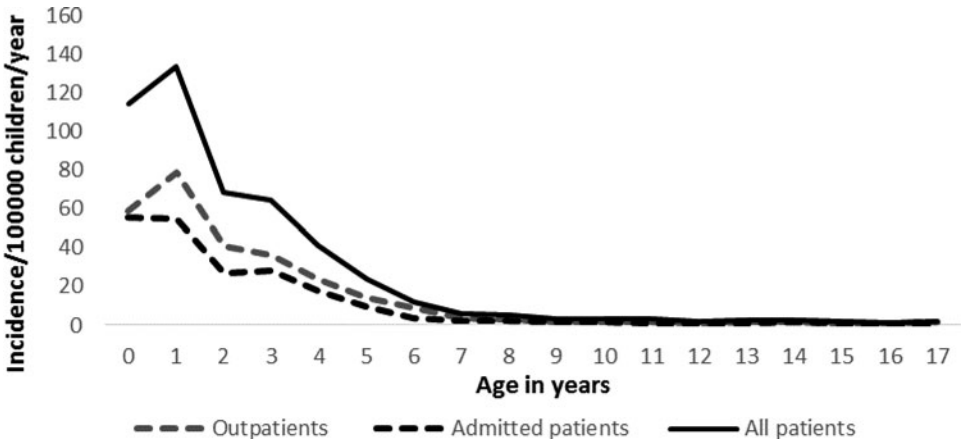

Fig. 3. Age-specific incidence of paediatric varicella hospitalizations in Denmark 2010–2016.

immunosuppression (or overall in children with underlying disease) and could thus be prevented by vaccination. Children with underlying medical conditions comprised 29·8% of admitted children and only 8·9% were immunosuppressed – well in line with results from other countries when taking varying definitions of underlying conditions in to account [15].

A major strength of our study is the application of a case–cohort design to compare hospitalized children with varicella to a random sample of the source population of all children 0–18 years of age in Denmark. The aim was to assess if children with underlying diseases were more likely to be hospitalized with varicella than the general population. We considered the application of a case–control design, but found that this was a problematic approach since varicella is a very common disease followed by immunity. We did not have information on ongoing or previous non-hospitalized varicella disease in the general population. Hence, we were unable to exclude children with a history of varicella (and therefore no longer at risk of varicella) from a control population. Among others, the case–cohort study differs from a standard case–control study because cases are allowed to be part of the reference group. This makes the case–cohort study a good representation of the corresponding cohort study and the estimated odds ratio a valid estimation of the risk ratio [27].

For all categories of underlying medical conditions, the odds for hospitalization with varicella were raised. This is not surprising since these children have closer contact to the secondary healthcare system regardless of varicella disease. The parents are likely to take contact to a hospital rather than a general practitioner or be referred more often. Children with immunosuppressive conditions are in higher risk of a serious course of varicella disease and make hospital contact when exposed to or developing varicella and are treated with acyclovir. We consider this to be the most important reason for the increased odds of being hospitalized for children with underlying disease. That the proportion of children with complications was not higher in children with underlying medical conditions could be an indication of the effectiveness of antiviral

https://doi.org/10.1017/S0950268817001777 Published online by Cambridge University Press

Table 4. *Results of logistic regression analysis of determinants for paediatric varicella hospitalization in Denmark 2010–2016*

Variable	Cases[a] $N = 1832$, N (%)	Referents $N = 17\,182$, N (%)	Univariable analysis[b] OR	95% CI	P value	Multivariable analysis[c] OR	95% CI	P value
Cancer disease	32 (1·75)	14 (0·1)	22·8	12·1–43·0	<0·001	17·0	8·6–33·3	<0·001
Autoimmune disease	49 (2·7)	34 (0·2)	14·6	9·4–22·7	<0·001	12·0	7·5–19·3	<0·001
Other immunosuppressive conditions	36 (2·0)	23 (0·1)	15·4	9·1–26·1	<0·001	6·7	3·7–12·2	<0·001
Central nervous system and neuromuscular disease	63 (3·4)	132 (0·8)	4·7	3·4–6·3	<0·001	3·6	2·6–5·0	<0·001
Heart disease	89 (4·9)	232 (1·4)	3·7	2·9–4·8	<0·001	2·4	1·8–3·2	<0·001
Lung disease	140 (7·6)	525 (3·1)	2·7	2·2–3·2	<0·001	2·1	1·7–2·6	<0·001
Metabolic diseases	16 (0·9)	32 (0·2)	4·7	2·6–8·6	<0·001	2·9	1·4–5·8	0·003
Hereditary diseases of the blood and haemophilia	9 (0·5)	13 (0·1)	6·6	2·8–15·4	<0·001	6·5	2·7–15·6	<0·001
Congenital syndromes	26 (1·4)	49 (0·3)	5·0	3·1–8·1	<0·001	2·6	1·5–4·4	<0·001
Atopic skin disease	39 (2·1)	113 (0·7)	3·3	2·3–4·8	<0·001	2·6	1·8–3·9	<0·001
History of prematurity	145 (7·9)	826 (4·8)	1·7	1·4–2·0	<0·001	1·4	1·1–1·7	0·001
Male gender	1000 (54·6)	8745 (50·9)	1·2	1·1–1·3	0·003	1·1	1·0–1·2	0·031
Not born in Denmark	109 (6·0)	480 (2·8)	2·2	1·8–2·8	<0·001	2·4	2·0–3·0	0·010

[a] Cases are outpatients and admitted patients.
[b] Controlled for matching factors (year of birth and year of hospitalization).
[c] Controlled for matching factors (year of birth and year of hospitalization) and region of residence.

Table 5 *Results of logistic regression analysis of determinants for paediatric varicella hospitalization ⩾1 day in Denmark 2010–2016*

Variable	Admitted patients $N = 783$, N (%)	Outpatients $N = 1049$, N (%)	Univariable analysis OR	95% CI	P value	Multivariable analysis[a] OR	95% CI	P value
Cancer disease	26 (3·3)	6 (0·6)	6·0	2·4–4·7	<0·001	10·0	3·9–25·6	<0·001
Autoimmune disease	31 (4·0)	18 (1·7)	2·4	1·3–4·3	0·003	3·8	2·0–7·2	<0·001
Other immunosuppressive conditions	21 (2·7)	15 (1·4)	1·9	1·0–3·7	0·056	–	–	–
Central nervous system and neuromuscular disease	36 (4·6)	27 (2·6)	1·8	1·1–3·0	0·019	–	–	–
Heart disease	43 (5·5)	46 (4·4)	1·3	0·8–1·9	0·276	–	–	–
Lung disease	61 (7·8)	79 (7·5)	1·0	0·7–1·5	0·836	–	–	–
Metabolic diseases	8 (1·0)	8 (0·8)	1·3	0·5–3·6	0·556	–	–	–
Hereditary diseases of the blood and haemophilia	4 (0·5)	5 (0·5)	1·1	0·3–4·0	0·918	–	–	–
Congenital syndromes	11 (1·4)	15 (1·4)	1·0	0·4–2·2	0·964	–	–	–
Atopic skin disease	21 (2·7)	18 (1·7)	1·6	0·8–3·0	0·157	–	–	–
History of prematurity	64 (8·2)	81 (7·7)	1·1	0·8–1·5	0·723	–	–	–
Age <1 year	194 (24·8)	205 (19·5)	1·4	1·1–1·7	0·007	1·9	1·5–2·4	<0·001
Male gender	434 (55·4)	566 (54·0)	1·1	0·9–1·3	0·531	–	–	–
Complications to varicella	525 (67·1)	326 (31·1)	4·5	3·7–5·6	<0·001	4·9	4·0–6·1	<0·001
Not born in Denmark	31 (4·0)	78 (7·4)	0·5	0·3–0·8	0·002	–	–	–

[a] Controlled for year and region of hospitalization.

medication against VZV. Male sex also increased the odds of a hospital contact; the reason for this overweight of males is not clear but has also been observed in other studies [13, 14].

With this study, we have provided baseline data on the epidemiology of hospitalized children with varicella in Denmark. Varicella vaccination has shown to be very effective against severe disease and the majority of the admissions described in this study could potentially be averted [4]. However, there are other important factors to be considered when discussing implementation of mass varicella vaccination. Varicella is most often a mild disease that most children will recover from without sequelae and it is followed by lifelong immunity. If vaccination coverage is not high enough, a rise in morbidity and mortality is a risk due to a shift in age of primary infection. Furthermore, the duration of immunity to varicella after vaccination is still not established and waning of immunity could also lead to a shift of varicella to the adult population. Studies from the USA and Germany does not indicate that a shift in age of primary infection has taken place so far [6, 9], but sufficient time since introduction of varicella vaccination may not have passed for this effect to be visible yet. A recent study of VZV seropositivity in >10 000 US air force recruits found that varicella vaccinated individuals were 24% less likely to be seropositive to VZV than those who experienced natural varicella infection. The odds of vaccinated individuals being seropositive decreased by 8% with each year since vaccination [28]. Furthermore, less circulation of wild varicella virus might lead to an increase in herpes zoster in adults according to the exogenous boosting theory proposed by Hope-Simpson [29]. Mathematical models have shown a potential rise in adult herpes zoster after childhood varicella vaccination [30]. The impact of mass varicella vaccination on the incidence of herpes zoster has been debated since the introduction of varicella vaccination in the childhood vaccination programme in the USA in 1995. The subject of exogenous boosting remains a concern that needs to be further studied as results of studies examining the effect of mass varicella vaccination on the incidence of herpes zoster in adults are not uniform [1, 31]. Some studies have shown a rise in herpes zoster incidence and hospitalizations since the introduction of varicella vaccination, while other studies have not demonstrated a rise or argue that the rise in incidence was apparent even before introduction of vaccination [1, 10, 11, 31–34]. Even if exogenous boosting does exist, it is still not clear to what extent it influences VZV epidemiology [35].

CONCLUSION

With this unique and nationwide study, we have provided a baseline from which to begin discussions on possible introduction of varicella vaccination in Denmark. The burden of paediatric varicella disease in Danish hospitals is considerable and by and large of the same magnitude as what has been found in other European countries comparable to Denmark. Some of these countries, like Germany, have chosen to implement universal varicella vaccination. Additional factors have to be taken in to account when considering implementation, but epidemiological data on the paediatric population, who bear the greatest burden, are the first important step in gathering evidence for a decision process.

SUPPLEMENTARY MATERIAL

The supplementary material for this article can be found at https://doi.org/10.1017/S0950268817001777.

ACKNOWLEDGEMENTS

The authors would like to thank Michael Galle and Jens Nielsen, Statens Serum Institute, for assistance.

This work was supported by an unrestricted grant from GlaxoSmithKline to the Department of Paediatrics and Adolescent Medicine, Rigshospitalet, Copenhagen, Denmark

DECLARATION OF INTEREST

I. G. Helmuth has received research funding for her Ph.D. study on varicella epidemiology through an unrestricted grant from GlaxoSmithKline to the Department of Paediatrics and Adolescent Medicine, Rigshospitalet, Copenhagen, Denmark. All other authors have no conflicts of interest to declare

REFERENCES

1. **Gershon AA, Gershon MD.** Pathogenesis and current approaches to control of varicella-zoster virus infections. *Clinical Microbiology Reviews* 2013; **26**(4): 728–743. doi: 10.1128/CMR.00052-13.
2. **Heininger U, Seward JF.** Varicella. *Lancet* 2006; **368** (9544): 1365–1376. doi: 10.1016/S0140-6736(06)69561-5.
3. **Nardone A, *et al.*** The comparative sero-epidemiology of varicella zoster virus in 11 countries in the European

region. *Vaccine* 2007; **25**(45): 7866–7872. doi: 10.1016/j.vaccine.2007.07.036.
4. **Marin M, *et al.*** Global varicella vaccine effectiveness: a meta-analysis. *Pediatrics* 2016; **137**(3): e20153741. doi: 10.1542/peds.2015-3741.
5. **World Health Organisation.** Varicella and herpes zoster: WHO position paper. *Weekly Epidemiogical Record* 2014; **89**(25): 265–287.
6. **Baxter R, *et al.*** Impact of vaccination on the epidemiology of varicella: 1995–2009. *Pediatrics* 2014; **134**(1): 24–30. doi: 10.1542/peds.2013-4251.
7. **Streng A, Liese JG.** Fifteen years of routine childhood varicella vaccination in the United States-strong decrease in the burden of varicella disease and no negative effects on the population level thus far. *Translational Pediatrics* 2014; **3**(4): 268–272. doi: 10.3978/j.issn.2224-4336.2014.10.02.
8. **Siedler A, Dettmann M.** Hospitalization with varicella and shingles before and after introduction of childhood varicella vaccination in Germany. *Human Vaccines & Immunotherapeutics* 2014; **10**(12): 3594–3600. doi: 10.4161/hv.34426.
9. **Siedler A, Arndt U.** Impact of the routine varicella vaccination programme on varicella epidemiology in Germany. *Euro Surveillance: Bulletin European Sur Les Maladies Transmissibles = European Communicable Disease Bulletin* 2010; **15**(13): pii=19530.
10. **Heywood AE, *et al.*** Varicella and herpes zoster hospitalizations before and after implementation of one-dose varicella vaccination in Australia: an ecological study. *Bulletin of the World Health Organization* 2014; **92**(8): 593–604. doi: 10.2471/BLT.13.132142.
11. **Marin M, Meissner HC, Seward JF.** Varicella prevention in the United States: a review of successes and challenges. *Pediatrics* 2008; **122**(3): e744–e751. doi: 10.1542/peds.2008-0567.
12. **Blumental S, *et al.*** Varicella paediatric hospitalisations in Belgium: a 1-year national survey. *Archives of Disease in Childhood* 2016; **101**(1): 16–22. doi: 10.1136/archdischild-2015-308283.
13. **Liese JG, *et al.*** The burden of varicella complications before the introduction of routine varicella vaccination in Germany. *The Pediatric Infectious Disease Journal* 2008; **27**(2): 119–124. doi: 10.1097/INF.0b013e3181586665.
14. **Hobbelen PHF, *et al.*** The burden of hospitalisation for varicella and herpes zoster in England from 2004 to 2013. *The Journal of Infection* 2016; **73**(3): 241–253. doi: 10.1016/j.jinf.2016.05.008.
15. **Helmuth IG, *et al.*** Varicella in Europe-A review of the epidemiology and experience with vaccination. *Vaccine* 2015; **33**(21): 2406–2413. doi: 10.1016/j.vaccine.2015.03.055.
16. **European Centre for Disease Prevention and Control.** Varicella-Guidance-2015.pdf. http://ecdc.europa.eu/en/publications/Publications/Varicella-Guidance-2015.pdf [accessed November 22, 2016].
17. **Schmidt M, Pedersen L, Sørensen HT.** The Danish Civil Registration System as a tool in epidemiology. *European Journal of Epidemiology* 2014; **29**(8): 541–549. doi: 10.1007/s10654-014-9930-3.
18. **Schmidt M, *et al.*** The Danish National Patient Registry: a review of content, data quality, and research potential. *Clinical Epidemiology* 2015; **7**: 449–490. doi: 10.2147/CLEP.S91125.
19. **Lynge E, Sandegaard JL, Rebolj M.** The Danish National Patient Register. *Scandinavian Journal of Public Health* 2011; **39**(7 Suppl.): 30–33. doi: 10.1177/1403494811401482.
20. Den nationale videnskabsetiske komité. dnvk.dk (http://www.dnvk.dk/CVK/Home/English.aspx). Accessed 7 November 2016.
21. **Guillén JM, *et al.*** Varicella paediatric hospitalizations in Spain. *Epidemiology and Infection* 2009; **137**(4): 519–525. doi: 10.1017/S0950268808001131.
22. **Dubos F, *et al.*** Epidemiology of hospital admissions for paediatric varicella infections: a one-year prospective survey in the pre-vaccine era. *Epidemiology and Infection* 2007; **135**(1): 131–138. doi: 10.1017/S0950268806006467.
23. **Pozza F, *et al.*** Impact of universal vaccination on the epidemiology of varicella in Veneto, Italy. *Vaccine* 2011; **29**(51): 9480–9487. doi: 10.1016/j.vaccine.2011.10.022.
24. **Widgren K, *et al.*** The burden of chickenpox disease in Sweden. *BMC Infectious Diseases* 2016; **16**(1): 666. doi: 10.1186/s12879-016-1957-5.
25. **Helmuth IG, *et al.*** Children hospitalized with varicella in Denmark: sensitivity of the National Patient Register. *The Pediatric Infectious Disease Journal* 2017; **36**(1): 31–35.
26. **Bonhoeffer J, *et al.*** Prospective surveillance of hospitalisations associated with varicella-zoster virus infections in children and adolescents. *European Journal of Pediatrics* 2005; **164**(6): 366–370. doi: 10.1007/s00431-005-1637-8.
27. **Rothman KJ, Greenland S, Lash TL.** *Modern Epidemiology*. Lippincott: Williams & Wilkins; 2008.
28. **Duncan JR, *et al.*** Varicella seroepidemiology in United States air force recruits: a retrospective cohort study comparing immunogenicity of varicella vaccination and natural infection. *Vaccine* 2017; **35**(18): 2351–2357. doi: 10.1016/j.vaccine.2017.03.054.
29. **Hope-Simpson RE.** The nature of herpes zoster: a long-term study and a new hypothesis. *Proceedings of the Royal Society of Medicine* 1965; **58**: 9–20.
30. **Brisson M, *et al.*** Exposure to varicella boosts immunity to herpes-zoster: implications for mass vaccination against chickenpox. *Vaccine* 2002; **20**(19–20): 2500–2507.
31. **Goldman GS, King PG.** Review of the United States universal varicella vaccination program: herpes zoster incidence rates, cost-effectiveness, and vaccine efficacy based primarily on the Antelope Valley Varicella Active Surveillance Project data. *Vaccine* 2013; **31**(13): 1680–1694. doi: 10.1016/j.vaccine.2012.05.050.
32. **Gil-Prieto R, *et al.*** Different vaccination strategies in Spain and its impact on severe varicella and zoster. *Vaccine* 2014; **32**(2): 277–283. doi: 10.1016/j.vaccine.2013.11.008.
33. **Hales CM, *et al.*** Examination of links between herpes zoster incidence and childhood varicella vaccination. *Annals of Internal Medicine* 2013; **159**(11): 739–745. doi: 10.7326/0003-4819-159-11-201312030-00006.

34. **Patel MS, Gebremariam A, Davis MM.** Herpes zoster-related hospitalizations and expenditures before and after introduction of the varicella vaccine in the United States. *Infection Control and Hospital Epidemiology* 2008; **29**(12): 1157–1163. doi: 10.1086/591975.

35. **Ogunjimi B, Van Damme P, Beutels P.** Herpes zoster risk reduction through exposure to chickenpox patients: a systematic multidisciplinary review. *PLoS ONE* 2013; **8**(6): e66485. doi: 10.1371/journal.pone.0066485.