Irish Medical Journal
Established 1867

Issue: Ir Med J; Vol 112; No. 7; P966

Varicella Related Hospital Admissions in Ireland

K.N. McCarthy, C. Ó Maoldomhnaigh, K.M. Butler, P.J. Gavin

Department of Paediatric Infectious Disease, Our Lady's Children's Hospital, Crumlin, Cooley Road, Crumlin, Dublin 12, D12 V004, Ireland

Abstract

Aim
The aim of this study was to evaluate trends in admissions for patients with primary varicella infection in Irish hospitals.
Methods
The Hospital Inpatient Enquiry System was evaluated from Irish hospitals from 2005-2016 for patients with primary varicella infection.
Results
There were 2717 admissions with primary varicella infection. The average annual number of admissions was 226 for an incidence of 4.87/100,000. Average length of stay (ALOS) was 5-days. Sixty-two (2.5%) patients required intensive-care with an ALOS of 26-days. The most common secondary diagnoses were cellulitis, volume-depletion and streptococcal infection. The number of admissions due to streptococcal infection and cellulitis significantly increased over the period.
Conclusion
Chickenpox places a consistent burden on Irish healthcare, accounting for in excess of 1100 acute and 160 intensive-care bed days annually. This study adds weight to the argument that universal varicella vaccine should be considered and provides baseline epidemiology to determine vaccine effectiveness in the future.

Introduction

Chickenpox is an acute self-limiting infection of childhood caused by varicella-zoster virus. Whilst chickenpox is often regarded as a mild illness characterized by vesicular rash, fever and malaise; significant complications may occur. Severe infection and complications including soft tissue infections, osteoarticular infection, pneumonia, and neurologic sequelae may require hospital admission.[1,2] Since 2011, in Ireland, hospitalised cases of chickenpox are notifiable to the Health Protection Surveillance Centre (HPSC). (1)[3] In 2015, 69 hospitalised cases were reported.[4] However the estimated incidence of 1.5/100,000 population is significantly lower than the range of 2.3-8.9 hospitalisations/100,000 reported from other countries.[5,6]

Chickenpox is a vaccine preventable illness. Varicella vaccine is safe with protective antibody levels in 85%-95% of vaccinated children after 1 dose and 99% after 2 doses.[7] World Health Organization recommends that countries where varicella is an important public health burden should consider introducing varicella vaccination into routine childhood immunisation programs.[8] However, most European countries have been slow to do so. At present, universal varicella vaccination is recommended nationally in six European countries and regionally in two.[9] Varicella vaccines are licensed in Ireland but not yet recommended as part of the primary immunization schedule but parents may seek vaccination privately. The European Centre for Disease Prevention and Control recommends that individual countries assess the epidemiological and socioeconomic impact of chickenpox.[11]

The primary aim of this study was to evaluate trends in hospital admissions for patients with chickenpox and to establish the burden of chickenpox related admissions on the Irish healthcare system.

Methods

The Republic of Ireland Hospital In-Patient Enquiry (HIPE) System is a computerized system that collects discharge information on day-case and inpatient admissions in public hospitals as a measure of hospital activity. Information collected includes demographic, clinical and administrative information on discharges and deaths. International Statistical Classification of Diseases and Related Health Problems, Tenth Revision 4th (2005-2008) and 6th (2009-2016) edition codes were systematically evaluated to identify those relevant to varicella infection. These included: B01 Varicella; B01.0 Varicella meningitis; B01.1 Varicella encephalitis; B01.2 Varicella pneumonia; B01.8 Varicella with other complications; and B01.9 Varicella without complication.

The study period was 12 years from 2005 to 2016. Data collected from all 56 Irish public hospitals, maternity hospitals and children's hospitals was abstracted from the HIPE database into Microsoft Excel. Data recorded included discharge diagnoses, secondary diagnoses, average age and length of stay and discharge outcome. All diagnoses were reviewed and subdivided into "predisposing conditions" or "complicating diagnoses" by the authors. Data extracted from the HIPE system in this study were anonymised aggregate data.

Statistical analysis was carried out using Prism6 software. Descriptive statistics were used in the analysis of patient characteristics. Data extracted from the HIPE system was reported as average per year therefore our results are presented as mean and standard deviation. Trends were examined using logistic regression analysis. Student's t-test was used to compare means. Population data for annual incidence calculations were extrapolated from the Irish National Census reports from 2006, 2011 and 2016.[12,13]

Results

Total admission and demographics

A total of 2717 admissions with any diagnosis of varicella-zoster infection were identified from 2005-2016. The average annual admission rate was 226 patients/year (range, 129-279, std.deviation 38.59). Annual hospital admissions did not significantly increase during the study period (p=0.19) (*Table 1*).

Group	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	p-value
Total	230	202	253	129	221	202	225	269	233	279	244	p=0.16
<1y	34	39	51	21	45	50	46	55	34	56	44	p=0.23
1-2y	62	62	82	30	80	48	58	76	66	66	68	p=0.69
3-4y	42	23	37	17	32	31	40	39	46	53	37	p=0.1
5-9 y	26	28	24	18	25	20	32	38	43	43	39	p=0.005
10-17	9	10	15	6	7	17	7	6	5	13	14	p=0.9
>18y	57	40	44	37	32	36	42	55	39	48	42	p=0.9
<18 y	173	162	209	92	189	166	183	214	194	231	202	p=0.11
Data are presented as annual mean number of admissions. Y =years												

Table 1: Total and annual admissions for patients with any listed discharge diagnosis of primary varicella zoster infection, 2005-2015

The average annual incidence of hospital admissions was 4.2/100,000 population (range, 3.8-4.83 /100,000, std.deviation 0.45). This is significantly higher than the crude average annual incidence of 1.42/100,000 population reported by the HPSC from 2012-2015 (p<0.001).[4]

Of total admissions, 81% (n=2199) were <18 years and 19% (n=518) were in the ≥18 years. Average admission rates in the <18 year and ≥18 year groups were 183 (range 92-231, std.deviation 35.12) and 43 (range 32-57, std.deviation 7.43) admissions/year, respectively. The age distribution of admissions were: 19% (514) <1 year; 28% (753) 1-2 years; 16% (438) 3-4 years; 14% (378) 5-9 years; 4% (116) 10-17 years; and 19% (518) ≥18 years. Only hospital admissions in the 5-9 year age group increased significantly over the study period (p=0.001). (*Table 1*) Of the total population 55% (1497) were male.

Level of care required

The average length of stay for the total population was 5-days (range, 3.6-6.1; std.deviation, 0.82). This did not increase significantly. HIPE reported 62 (2.5%) ICU admissions over the 12-year period. The average length of ICU stay was 26 days (range, 0-60.7; std.deviation, 21.13). This represents an average of 161 ICU bed days annually in patients with varicella infection. The average length of stay for non-ICU admissions was 4 days (range, 3.3-5.6; std.deviation, 0.77). This represents an average of 1130 inpatient bed days annually. The average length of stay was significantly shorter in those <18 years compared to the ≥18 years; 3 days (range, 2.8-4.1; std.deviation, 0.34) vs. 10 days (range, 5.1-20.6; std.deviation, 4.34) (p=0.002) representing an average of 605 inpatient bed days/year among those <18 and 472 among those ≥18 years. The average cost per in-patient stay per night in Irish public hospitals is €878.00 and the median daily cost of intesnive care unit admission is €2,205.00. The estimated cost to the Irish healthcare system for inpatient admissions alone as a result of primary varicella infection is therefore in excess of €1.34 million per anum[14,26].

Underlying diagnoses

Ninety-one (3.3%) admissions had discharge diagnoses that could be classified as predisposing conditions. These included: transplanted organs or tissues, 36; lymphoid leukaemia, 29; nephrotic syndrome, 6; and the need for prophylactic procedures otherwise unspecified, 20. In those <18, 2% (44) had a predisposing diagnosis or need for prophylaxis compared with 9% (47) of those ≥18 years.(*Table 2*).

Indication	Total (n=2487)	<18 Years (n=2015)	>18 Years (n=472)
Transplanted organs or tissues	36	9	27
Lymphoid Leukaemia	29	20	9
Nephrotic Syndrome	6	6	0
Need for prophylactic procedures	20	9	11
Total (%)	91 (3.7%)	44 (2.2%)	47 (10%)

Table 2: Predisposing conditions coded for in admissions with any listed discharge diagnosis of primary varicella zoster infection, 2005-2015

Complications

A complicating diagnosis was coded for 757 (28%) admissions. The most common complications were cellulitis, volume depletion and streptococcal infection (*Table* 3).

Complication	n	% total complications
Cellulitis	246	32.40%
Volume Depletion	175	23.10%
Streptococcus Infection	145	19.10%
Problems related to lifestyle	59	7.50%
Convulsions	40	5.30%
Upper Respiratory Tract Infection	35	4.60%
Fluid/Electrolyte disorders	19	2.50%
Gastroenteritis	18	2.40%
Nausea & Vomiting	13	1.70%
Disorders of the orbit	7	0.90%

Table 3: Complicating diagnoses coded for in admissions with any listed discharge diagnosis of primary varicella zoster infection, 2005-2015

The number of admissions complicated by streptococcal infection increased steadily from 6/year in 2005 to 26/year in 2016 (p=0.005, 95% CI 0.8-2). Similarly, the number of admissions due to cellulitis increased (p<0.001, 95% CI 1.9-3.9). Other complicating diagnoses did not change significantly and there were no deaths during the study period.

Discussion

The present study is the first comprehensive evaluation, to date, of trends in hospital admissions related to

chickenpox in Ireland. We report an average annual incidence of 4.87 varicella related hospital admissions/100,000 population which is significantly higher than the incidence of 1.5/100,000 population reported as a notifiable disease in 2015 to the HPSC.[4] The average annual incidence of hospitalisation in our study is within the range (2.3-8.9 /100,000 population) reported in other European studies using similar case definitions.[6,5] The average length of hospital stay of 5 days is comparable to that described elsewhere (2.7-7 days).[5,15,18] Infants and young children make up the majority of admissions; 47% are < 3-years old and 76% < 10-years old. The age distribution is in keeping with early epidemiologic studies where almost 90% of children in a susceptible population were infected with chickenpox by age 10, and that reported recently in England (79.4% of admissions < 10 years old).[5,15] In contrast to recent descriptions in the United Kingdom, no reduction in the age of acquisition of chickenpox was seen in our study.[16] A significant increase in chickenpox related hospital admissions was observed in the 5 to 9 year age group. The male predominance (55%) among chickenpox related hospital admissions reflects a similar trend towards increased hospitalizations and more severe disease in males reported elsewhere and potentially suggests a differential gender specific immune response to varicella infection.

The majority (96.3%) of chickenpox related hospital admissions in Ireland occurred in those without underlying conditions. Similarly, 85% of children admitted with varicella in Irish paediatric hospitals in a smaller 2007 surveillance study were otherwise healthy.[19] Therefore, the major burden on acute inpatient beds is due to illness in previously healthy, immuncompetent individuals in whom live attenuated vaccination is not contraindicated.

The complication rate of 30% in our study is lower than rates of 40%-79% reported elsewhere.[19,22] Skin and soft tissue infections were the most commonly encountered complications, emphasising that bacterial super-infection remains an important consideration in the assessment of patients with chickenpox. The increase in chickenpox admissions complicated by streptococcal infection and cellulitis reflects the parallel increase in invasive group A *Streptococcus* infection reported from 2012-2014.[4] Preceding chickenpox infection is recognised as the most significant risk factor for invasive group A streptococcal infection in childhood[19,20] . Universal varicella vaccination in childhood is associated with a reduction in severe varicella infections and specifically invasive streptococcal infection.[21] Additional data demonstrates a reduction in general practitioner and emergency department visits further reducing the burden of varicella on the healthcare system.[25] In contrast to other studies, neurologic complications were relatively under-represented.[17,19,,23]
Adults accounted for fewer chickenpox related admissions however significantly longer hospital stays suggest a more complicated disease course. Concerns regarding a potential shift in the age distribution to increase varicella infection and overall morbidity among non-immune adults contributed to a reluctance to adopt childhood vaccination in the United Kingdom and adult vaccination in the United States.[25] Nevertheless, disease modeling and post-vaccine surveillance dispute this and suggest herd immunity results from universal vaccination.

Several study limitations need to be considered. Data was sourced from a database that relies on correct coding and interpretation of medical records. A recent audit found that HIPE data appeared to underrepresent clinical complexity by approximately 2% of total activity when compared to international counterparts.[26] The HIPE database includes discharge data from all Irish public hospitals, including private beds in public hospitals, but does not include data from private hospitals. There are approximately 1,926 beds in Irish private hospitals (estimated 13.6% of total beds), therefore our data may underestimate the true burden of admissions, particularly among adult patients. While the present study includes discharge data from maternity units, data protection policy precluded its separate analysis. Similarly, while detailed group reports with average data were provided, absence of individual patient and hospital level data potentially limited the analysis. Furthermore, because data from each HIPE discharge record represents one episode of care, individual patients may have had multiple admissions, making this data useful for interpretation of hospital activity relating to a specific diagnosis but not incidence of disease. The true burden of infection may also be underestimated as patients admitted with complications following acute infection may not be coded for preceding varicella infection on readmission. This may explain the relative paucity of reports of neurologic complications. HIPE data does not take account of the burden of infection on primary care, emergency departments, or the socioeconomic burden of infection. However, our results are comparable with international studies and we believe accurately reflect the burden of chickenpox on Irish hospitals.

The present study is a comprehensive examination of trends in chickenpox admissions in Irish hospitals. The calculated incidence of 4.87 admissions/100,000 population is significantly higher than previous local estimates based on laboratory-confirmed cases. In the present study, chickenpox accounted for an average of 1130 acute hospital and 161 ICU bed days annually in Irish hospitals and is associated with an estimated cost of €1.34 million.

As such, our study represents a more accurate estimate of the burden of chickenpox related admissions on the Irish inpatient healthcare system than existing estimates that rely on laboratory confirmed cases alone. While immunocompromised patients are at high risk, the burden of severe infection and complications falls disproportionately on previously healthy children in whom varicella vaccination is safe and effective. The present study again demonstrates that a universal vaccination strategy, rather than one targeting high-risk patients, is the only one likely to significantly reduce severe and complicated infections and the burden placed on already strained inpatient and intensive care beds in Irish hospitals. And finally, this study provides more accurate data on baseline epidemiology necessary to properly evaluate the potential benefit and effectiveness of varicella immunisation. As such, it should contribute to the discussion regarding inclusion of varicella vaccine in the national immunization schedule in Ireland.

Acknowledgements:
We would like to thank the Healthcare Pricing Office, Ireland for providing data from the Hospital Inpatient Enquiry (HIPE) scheme for analysis in this study.

Declaration of Conflict Of Interest:
None

Funding:
None

Corresponding Author:
Dr. Karen McCarthy
Department of Paediatric Infectious Disease,
Our Lady's Children's Hospital Crumlin,
Cooley Road,
Crumlin,
Dublin 12,
D12 V004,
Ireland
Email: karen.n.mccarthy@gmail.com
Fax: 00353 1 4282760

References:

1. Liese JG, Grote V, Rosenfeld E, Fischer R, Belohradsky BH, Kries R V. The burden of varicella complications before the introduction of routine varicella vaccination in Germany. Pediatr Infect Dis J. 2008;27(2):119–24.
2. Turel O, Bakir M, Gonen I, Hatipoglu N, Aydogmus C, Hosaf E, Siraneci R. Children hospitalized for varicella: Complications and cost burden. Value Heal Reg Issues. 2013;2(2):226–30.
3. Health Protection Surveillance Centre. Notifiable Diseases and their respective causative pathogens. [Internet]. 2016 [cited 2017 May 6]. Available from: http://www.hpsc.ie/notifiablediseases/listofnotifiablediseases/File,678,en.pdf
4. Health Protection Surveillance Centre. HPSC 2015 Annual Epidemiological Report [Internet]. 2016 [cited 2017 May 6]. p. 53–4. Available from: http://www.hpsc.ie/abouthpsc/annualreports/File,15956,en.pdf
5. Hobbelen PHF, Stowe J, Amirthalingam G, Miller L, van Hoek AJ. The burden of hospitalisation for varicella and herpes zoster in England from 2004 to 2013. J Infect [Internet]. 2017 May 5;73(3):241–53. Available from: http://dx.doi.org/10.1016/j.jinf.2016.05.008
6. de Melker H, Berbers G, Hahné S, Rümke H, van den Hof S, de Wit A, et al. The epidemiology of varicella and herpes zoster in The Netherlands: Implications for varicella zoster virus vaccination. Vaccine. 2006;24(18):3946–52.
7. Merck. Highlights of prescribing information for Varivax ®. [Internet]. Vol. 2. 2017. Available from: http://www.merck.com/product/usa/pi_circulars/v/varivax/varivax_pi.pdf
8. World Health Organisation. Varicella and herpes zoster vaccines: WHO position paper. Wkly Epidemiol Rec Relev épidémiologique Hebd [Internet]. 2018;93(25):73–96. Available from: http://www.who.int/wer

9. European Centre for Disease Prevention and Control. Varicella Vaccine in the European Union [Internet]. 2014. Available from: http://ecdc.europa.eu/en/publications/Publications/Varicella-guidance-2014-consultation.pdf
10. Health Service Executive National Immunisation Advisory Committee. Immunisation Guidelines of Ireland Chapter 23 Varicella- Zoster. 2015.
11. European Centre for Disease Prevention and Control. ECDC Guidance - Varicella vaccination in the European Union. 2015. 1-58 p.
12. CSO. Central Statistics Office. Census of Population 2016, Preliminary Results [Internet]. Census of Population 2016 - Preliminary Results. 2016 [cited 2017 Aug 2]. Available from: http://www.cso.ie/en/releasesandpublications/ep/p-cpr/censusofpopulation2016-preliminaryresults/intro/
13. CSO. Population 1841-2011 [Internet]. Population by sex and census year. 2011 [cited 2017 Aug 2]. Available from: http://www.cso.ie/multiquicktables/quickTables.aspx?id=cna13
14. McLaughlin, A. M., Hardt, J., Canavan, J. B. and Donnelly, M. B. (2012) 'Determining the economic cost of ICU treatment: a prospective "micro-costing" study.', *Intensive care medicine*. doi: 10.1007/s00134-009-1622-1.
15. Dubos F, Granbastian B, Hue V, Martinot A. Epidemiology of hospital admissions for paediatric varicella infections: a one-year prospective survey in the pre-vaccine era. Epidemiol Infect [Internet]. 2007 Jan 2;135(1):131–8. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2870539/
16. Brisson M, Edmunds WJ, Law B, Gay NJ, Walld R, Brownell M, Roose L, De Seres G. Epidemiology of varicella zoster virus infection in Canada and the United Kingdom. Epidemiol Infect [Internet]. 2001 Oct;127(2):305–14. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2869750/
17. Gowin E, Wysocki J, Michalak M. Don't forget how severe varicella can be: Complications of varicella in children in a defined Polish population. Int J Infect Dis [Internet]. 2017 May 8;17(7):e485–9. Available from: http://dx.doi.org/10.1016/j.ijid.2012.11.024
18. Glode Helmuth I, Broccia MD, Glenthøj JP, Harder K, Jensen L, von Linstow ML, Poulsen A, Mølbak, K. Children Hospitalized With Varicella in Denmark: Sensitivity of the National Patient Register. Pediatr Infect Dis J [Internet]. 2017;36(1). Available from: http://journals.lww.com/pidj/Fulltext/2017/01000/Children_Hospitalized_With_Varicella_in_Denmark_.10.aspx
19. Cameron JC, Allan G, Johnston F, Finn A, Heath PT, Booy R. Severe complications of chickenpox in hospitalised children in the UK and Ireland. Arch Dis Child [Internet]. 2007 Dec 29;92(12):1062–6. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2066097/
20. Lin F, Hadler JL. Epidemiology of Primary Varicella and Herpes Zoster Hospitalizations: The Pre-Varicella Vaccine Era. J Infect Dis [Internet]. 2000 Jun 1;181(6):1897–905. Available from: http://dx.doi.org/10.1086/315492
21. Siedler A, Dettmann M. Hospitalization with varicella and shingles before and after introduction of childhood varicella vaccination in Germany. Hum Vaccines Immunother. 2014;10(12):3594–600.
22. Wormsbecker AE, Wang J, Rosella LC, Kwong JC, Seo CY, Crowcroft NS, Deeks S. Twenty years of medically-attended pediatric varicella and herpes zoster in Ontario, Canada: A population-based study. PLoS One. 2015;10(7).
23. Rack AL, Grote V, Streng A, Belohradsky BH, Heinen F, von Kries R, Liese JG. Neurologic Varicella Complications Before Routine Immunization in Germany. Pediatr Neurol. 2010;42(1):40–8.
24. Papaloukas O, Giannouli G, Papaevangelou V. Successes and challenges in varicella vaccine. Ther Adv Vaccines [Internet]. 2014 Mar;2(2):39–55. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3991154/
25. Davis MM, Patel MS, Gebremariam A. Decline in Varicella-Related Hospitalizations and Expenditures for Children and Adults After Introduction of Varicella Vaccine in the United States. Pediatrics [Internet]. 2004 Sep 1;114(3):786 LP-792. Available from: http://pediatrics.aappublications.org/content/114/3/786.abstract
26. Pavillion Health. National Audit of Admitted Patient Information in Irish Acute Hospitals. 2016;(September). Available from: http://www.hpo.ie/latest_hipe_nprs_reports/Pavilion_Report_National_Audit__Admitted_Patient_Info_Sept_2016.pdf