Severe complications associated with varicella: Province of Quebec, April 1994 to March 1996

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OBJECTIVE: To determine the frequency and severity of serious complications associated with varicella in Quebec; the frequency and severity of cases of congenital varicella; and hospital costs associated with hospitalizations for varicella.
STUDY DESIGN: All hospitalizations related to varicella were identified through the use of a hospital data bank and pertinent data were collected from hospital records.
SETTING: Province of Quebec with a population of 6,895,960 people.
STUDY POPULATION: All cases with a principal or secondary diagnosis of varicella hospitalized in Quebec between April 1, 1994 and March 31, 1996.
OUTCOME MEASURES: Types of complications and reason for hospitalization, risk of complications and calculation of associated costs were studied.
RESULTS: Nine hundred nine eligible hospitalizations were identified between April 1, 1994 and March 31, 1996. In all, 583 (64.1%) hospitalizations were for the treatment of complications, 127 (14.0%) for administration of intravenous acyclovir and 199 (21.9%) for supportive care. Healthy people accounted for 644 (70.8%) hospitalizations and immunosuppressed individuals for 136 (15.0%). Among children, one-half of the principal complications were skin infections, while 13.5% and 8.4% of principal complications were pneumonia and neurological complications, respectively. Among adults, the most common complication was pneumonia, with a rate of 43.5%, followed by thrombocytopenia and skin infections, with rates of 22.2% and 14.8%, respectively. The complication rate was 29.2 cases/10,000 cases of varicella.
CONCLUSIONS: Although perceived as a benign childhood disease by the general population, varicella may be accompanied by severe complications. Morbidity associated with varicella is one of the elements that must be considered when evaluating the usefulness of varicella vaccine.

Key Words: *Communicable diseases control; Disease notification; Population surveillance; Public health; Varicella*

Complications graves de la varicelle : Province de Québec, Avril 1994 à Mars 1996

OBJECTIF : Déterminer la fréquence et la gravité des complications sérieuses de la varicelle au Québec, la fréquence et la gravité des cas de varicelle congénitale et les coûts hospitaliers associés aux hospitalisations pour la varicelle.
MODÈLE DE L'ÉTUDE : Toutes les hospitalisations associées à la varicelle ont été identifiées à partir des banques de données hospitalières et des données pertinentes ont été recueillies dans les dossiers hospitaliers.
CONTEXTE : Province de Québec à partir d'une population de 6 895 960 personnes.
POPULATION ÉTUDIÉE : Tous les patients ayant reçu un diagnostic principal ou secondaire de varicelle, hospitalisés

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au Québec entre le 1er avril 1994 et le 31 mars 1996.
MESURES PARAMÉTRIQUES : Type de complications et raison de l'hospitalisation, risque de complications et calcul des coûts associés.
RÉSULTATS : Neuf cent neuf hospitalisations admissibles ont été recensées entre le 1er avril 1994 et le 31 mars 1996. En tout, 583 (64,1 %) des hospitalisations ont été justifiées par le traitement de complications, 127 (14,0%) pour l'administration d'acyclovir par voie intraveineuse et 199 (21,9 %) pour un traitement d'appoint. Les personnes par ailleurs en bonne santé représentaient 644 (70,8 %) des hospitalisations et les sujets immunodéprimés, 136 (15,0 %). Parmi les enfants, la moitié des cas de complications principales étaient des infections cutanées, alors que 13,5 % et 8,4 % des complications principales étaient respectivement la pneumonie et les complications neurologiques. Parmi les adultes, les complications les plus courantes ont été la pneumonie, avec un taux de 43,5 %, suivie de la thrombocytopénie et de l'infection dermatologique, avec des taux de 22,2 et 14,8 %, respectivement. Le taux de complication a été de 29,2 cas/10 000 cas de varicelle.
CONCLUSIONS : Bien que perçue comme une maladie infantile bénigne par la population générale, la varicelle peut s'accompagner de complications graves. La morbidité associée à la varicelle est l'un des éléments dont on doit tenir compte lorsque l'on évalue l'utilité du vaccin contre la varicelle.

Varicella is usually a benign disease in children. More severe forms of the disease and complications occur proportionately more frequently among adolescents, adults and immunosuppressed people (1-3). In the United States, the average annual number of hospitalizations for varicella has been estimated at 3837, 70% of which were among children under the age of 10 years (1). The risk of hospitalization increases with age: 42 and 127 hospitalizations/10,000 cases were reported for 15- to 19-year olds and for adults 20 years old and over, respectively, compared with about 10 hospitalizations/10,000 for children aged 14 years and younger (1).

According to an American study of 4884 cases of varicella carried out over two years in the early 1990s, 100 presented at least one complication, for a rate of 205 cases with complications/10,000 cases of varicella, and 30 had to be hospitalized (hospitalization rate 61/10,000) (2).

Among people 19 years of age or younger, skin and soft tissue infections were predominant, and were the cause of over 50% of hospitalizations; among adults, varicella pneumonia was the most common complication. Among both groups, encephalitis, dehydration and hepatitis were among the other, less common causes of hospitalization (2).

In Canada, the *Canadian Medical Association Journal* (4) noted a rate of 2.3 hospitalizations/100,000 in 1984, with hospitalization rates of 27.5/100,000 among infants younger than one year of age, 17.5/100,000 among one- to four-year olds and 5.5/100,000 among five- to 14-year olds (4). In a university-affiliated paediatric hospital in Calgary, Alberta, serving a population of 1.2 million and with approximately 6500 admissions/year, 165 children were hospitalized for varicella (2.6 cases of varicella/1000 admissions) between January 1, 1983 and December 31, 1992 (5).

In the present study, we evaluated the morbidity associated with varicella using hospitalized cases and costs related to these hospitalizations.

PATIENTS AND METHODS

Identifying hospitalizations: The Med-Echo database is the hospital discharge data registry in which all admissions to Quebec acute care hospitals are entered. With the authorization of the directors of professional services, the authors asked the archives department of each hospital in the province of Quebec to search their local Med-Echo database for all hospitalizations having code 052 as the principal or secondary diagnosis from April 1, 1994 to March 31, 1996. No discrepancy was noted between a preliminary list that was received from the provincial database and the list prepared by each hospital.

The Immunization Monitoring Program, ACTive (IMPACT) is a network of 11 Canadian paediatric hospitals, which monitors vaccine-preventable diseases (6). At the three Quebec participating hospitals, a nurse from the research team compared the list drawn up from the Med-Echo database with the one obtained from the IMPACT file to identify hospitalizations not found in the Med-Echo database.

Data collection: A research nurse reviewed all hospitalization records; each hospitalization was validated and pertinent data were collected using a standardized questionnaire. If a varicella-associated hospitalization involved a pregnant woman, the newborn's file was also examined for congenital varicella.

Definitions of certain variables: Complications were classified as major or minor. Major complications were, in order of decreasing importance, necrotizing fasciitis, bacteremia or septicemia, neurological complications and pneumonia. Minor complications were skin infections (excluding necrotizing fasciitis), hepatitis and thrombocytopenia. For patients presenting with a major and a minor complication, the major complication became the principal one. For those presenting more than one major complication, the previously mentioned order of importance determined the principal complication.

Hospitalizations were divided hierarchically into three mutually exclusive groups according to the reason for hospitalization: complication associated with varicella; in the absence of complications, treatment with intravenous acyclovir; and supportive care in the absence of complications and acyclovir treatment.

The patients' state of health was determined according to three categories: healthy if no chronic health problems were noted in the file; immunosuppressed in one of the following circumstances – currently receiving chemotherapy or radiotherapy for cancer, immunosuppression treatment for transplantation, oral or intravenous corticotherapy, excluding topical or inhaled corticosteroids, congenital immune deficiency, or HIV infection regardless of level of immunodeficiency; or having another health condition.

TABLE 1
Number of hospitalizations for varicella infection by age group, Quebec, April 1994 to March 1996

Age groups (years)	N (%)	Cumulative %
<1	107 (11.8)	11.8
1	125 (13.8)	25.6
2	116 (12.8)	38.4
3	92 (10.1)	48.5
4	63 (6.9)	55.4
5 to 9	175 (19.2)	74.6
10 to 17	43 (4.7)	79.3
18 and older	188 (20.7)	100
Total	909 (100)	–

To calculate age-specific rates of complication, the annual number of cases with complications obtained in the study for each age group was used as the numerator (subsequent hospitalizations in the same hospital or in a specialized centre were removed from the initial numbers), and the annual number of varicella cases, using incidence rates obtained by Boulianne et al (7) for age groups under 10 years of age, was used as the denominator. For those aged 10 years and older, incidence rates calculated in the United States by the National Center for Health Statistics (USA) were used and corrected for under-reporting (1).

Calculation of hospitalization costs: Hospitalization costs were calculated using the hospital performance evaluation system of the Ministère de la Santé et des services sociaux du Québec (8). This calculation is based on the Niveau d'intensité relative des ressources utilisées (NIRRU), an index reflecting the relative use of resources for each hospitalization classified according to its All-Patient Refined Diagnostic-Related Group (APR-DRG). These APR-DRGs comprise 1530 groups of clinically homogeneous patients requiring an equivalent level of resources. They are based on diagnosis, severity and probability of poor outcome.

The NIRRU was based on costs per APR-DRG for typical patients established in Maryland in 1994. The cost for each APR-DRG was divided by the mean cost for all hospitalizations to obtain a relative weight, where 1.00 corresponded to the mean. This index was then adjusted to take into account the differences in lengths of stay between Maryland and Quebec.

Taking into account the net costs by field of activity (emergency room, outpatient clinics, hospitalizations, etc) in each acute care hospital in Quebec, the average cost of an acute care hospitalization can be calculated by dividing the total cost of episodes of acute care hospitalization by the total number of hospitalizations ($2817 in 1995). By multiplying the NIRRU attributed by the Med-Echo system to each hospitalization by the average provincial cost of acute care hospitalizations, the cost of each hospitalization was calculated (8).

Statistical analysis: Data collected were entered and analysed using Epi-Info 6.04b (Centers for Disease Control and Prevention, USA).

Ethical considerations: The Montreal Public Health Department research ethics committee approved the project.

TABLE 2
Distribution of hospitalizations for varicella by reason for hospitalization, health status and age category, Quebec, April 1994 to March 1996

Reason for hospitalization	Healthy n (%)	Immuno-suppressed n (%)	Other condition n (%)	Total n (%)
Complications				
<18 years	388 (43)	29 (3)	51 (6)	468 (51)
18 years and older	85 (9)	17 (2)	13 (1)	115 (13)
Intravenous acyclovir				
<18 years	16 (2)	59 (7)	9 (1)	84 (9)
18 years and older	14 (1)	26 (3)	3 (<1)	43 (5)
Supportive care				
<18 years	118 (13)	3 (<1)	47 (5)	168 (18)
18 years and older	23 (2)	2 (<1)	6 (<1)	31 (3)
Total	644 (71)	136 (15)	129 (14)	909 (100)

RESULTS

Eligibility: A total of 1103 hospitalizations were in the Med-Echo database. Nineteen patient records could not be consulted. Of the 1084 hospitalizations reviewed, 183 patients were considered ineligible: 140 because the varicella at admission was not linked to the reason for hospitalization or because the varicella during hospitalization had no impact on hospital stay; 11 because patients did not live in Quebec; and 32 because the 052 code was wrong.

Among the 901 eligible hospitalizations, varicella was the principal diagnosis for 488 (54.2%) and the first secondary diagnosis for 232 (25.8%). Varicella was the principal diagnosis or one of the first three secondary diagnoses for more than 98% of patients.

Another eight episodes (patients in a chronic care ward that could not have been found in the Med-Echo database) were registered in IMPACT. It was decided to include these patients because they were treated for complications or received intravenous acyclovir. On the other hand, the exhaustivity of IMPACT was not verified. In all, 706 (79.8%) children (under age 18 years) and 179 (20.2%) adults (age 18 years or older) needed 909 hospitalizations: 863 people were hospitalized once, seven hospitalized in a primary care hospital and then transferred to a specialized centre; 14 were hospitalized twice in the same hospital; and one was hospitalized four times in the same hospital.

Analysis of hospitalizations: The distribution of hospitalizations by age is shown in Table 1. The average age of children and adults was 3.6 and 33.9 years, respectively. Of 909 hospitalizations, 583 (64.1%) were to treat one or several complications, 127 (14.0%) to receive intravenous acyclovir and 199 (21.9%) to give supportive care (Table 2). Of the 644 hospitalizations among healthy people, 473 (73.4%) were to treat complications, 30 (4.7%) were to receive intravenous acyclovir and 141 (21.9%) were to give supportive care compared with 46

TABLE 3
Distribution of principal complications from varicella infection by age category, Quebec, April 1994 to March 1996

	Principal			Total
Complications	**<18 years, n (%)**	**≥18 years, n (%)**	**All ages, n (%)**	**All ages, n (%)**
Skin infections				
Cellulitis	127 (27.1)	6 (5.2)	133 (22.8)	140 (18.6)
Impetigo	92 (19.7)	12 (10.4)	104 (17.8)	116 (15.4)
Scarlet fever	10 (2.1)	0 (0.0)	4 (0.7)	25 (3.3)
Skin abscess	4 (0.9)	0 (0.0)	4 (0.7)	10 (1.3)
Necrotizing fasciitis	6 (1.3)	0 (0.0)	6 (1.0)	6 (0.8)
Other infections				
Pneumonia	63 (13.5)	48 (41.7)	111 (19.0)	134 (17.8)
Bacteremia	20 (4.3)	4 (3.5)	24 (4.1)	26 (3.5)
Osteoarticular infection	5 (1.1)	0 (0.0)	5 (0.9)	9 (1.2)
Neurological complications				
Ataxia	22 (4.7)	1 (0.9)	23 (3.9)	23 (3.1)
Encephalitis	14 (3.0)	3 (2.6)	17 (2.9)	17 (2.3)
Aseptic meningitis	4 (0.9)	0 (0.0)	4 (0.7)	4 (0.5)
Guillain-Barré syndrome	0 (0.0)	2 (1.7)	2 (0.3)	2 (0.3)
Hepatitis	12 (2.6)	11 (9.6)	23 (3.9)	41 (5.4)
Thrombocytopenia	22 (4.7)	24 (20.9)	46 (7.8)	80 (10.6)
Various				
Febrile convulsions	25 (5.3)	0 (0.0)	25 (4.3)	36 (4.8)
Dehydration	20 (4.3)	0 (0.0)	20 (3.4)	35 (4.6)
Antihistamine intoxication	3 (0.6)	0 (0.0)	3 (0.5)	4 (0.5)
Others	19 (4.1)	4 (3.5)	23 (3.9)	45 (6.0)
Total	468 (100)	115 (100)	583 (100)	753 (100)

TABLE 4
Risk of complications from varicella infection, Quebec, April 1994 to March 1996

Age group (years)	Population	Incidence cases/ 1000 person years	Cases/year	Cases with complication/two years	Cases with complication/10,000 cases
Birth to 4	470,642	105.1	49,464	319	32.2
5 to 9	453,444	80.5	36,502	109	14.9
10 to 14	475,360	17.5	8333	29	17.4
15 to 19	497,534	2.9	1447	9	31.1
20 or older	5,440,602	0.3	1795	104	289.7
Total	7,337,582	13.3	97,541	570	29.2

(33.8%), 85 (62.5%) and five (3.7%), respectively, for the 136 hospitalizations of immunosuppressed people.

The median delay between the onset of illness and hospitalization was three days for children and adults (one day for immunosuppressed children). The median hospital stay was three days for children and four days for adults. Approximately 12% of children stayed in hospital more than seven days compared with 25.3% of adults. Although almost all the immunosuppressed children and close to 90% of immunosuppressed adults received intravenous acyclovir, slightly less than one-quarter of all children received intravenous acyclovir; this proportion rose to almost 60% among adults.

Complications analysis: Five hundred seventy people were hospitalized 583 times for complications and presented with 753 complications (Table 3). Among the 753 complications, 297 (39.4%) were skin infections, 134 (17.8%) pneumonia, 80 (10.6%) thrombocytopenia and 46 (6.2%) neurological complications. Among children, one-half of the complications were skin infections, followed by pneumonia and neurological complications, 13.5% and 8.4% of principal complications, respectively. Among adults, the most common complications were pneumonia (43.5% of complications), thrombocytopenia (22.2% of complications) and skin infections (14.8% of complications).

TABLE 5
Average cost of hospitalizations by type of hospitalization and health condition, and age category, Quebec, April 1994 to March 1996

Reason for hospitalization	Healthy	Immunosuppressed	Other condition	All conditions (range)
Complications				
< 18 years old	2216	3356	2253	2299 (483-16,918)
18 years old or older	2559	5133	5034	3101 (1049-13,805)
Intravenous acyclovir				
< 18 years old	4416	3435	2878	3543 (1049-17,252)
18 years old or older	1852	5581	1833	4205 (1049-33,132)
Supportive care				
< 18 years old	1645	2673	2261	1829 (545-7106)
18 years old or older	1489	NA	2561	1819 (544-4340)
All reasons	2168	3993	2508	2504 (483-33,132)

NA Not applicable

Risk of complications: The overall risk of complication was 29.2 cases with complications/10,000 cases of varicella (Table 4). Although the number of varicella cases and complications among adults aged 20 years and older was much lower than among the birth to 19 years age group, the rate of complications was 10 times greater (289.7 versus 24.3 cases with complications/10,000 cases).

Pregnancy, varicella and congenital varicella: During the two-year study period, 25 women were hospitalized for varicella during pregnancy. Their median age was 28 years (range 15 to 35 years) and the median gestational age was 30 weeks (range nine to 40 weeks). In all, 11 women (44%) presented with a complication, seven of whom had pneumonia. Eight (32%) received intravenous acyclovir. No cases of congenital varicella were reported among the 23 of 25 records of newborns that could be reviewed.

However, one case of congenital varicella was discovered upon reviewing a newborn's file in which the 052 code was entered in the hospitalization summary. The diagnosis was made postpartum. The mother had had varicella around the 20th week of gestation but had not been hospitalized.

Deaths: Five deaths associated with complications were identified. An 11-year-old girl with asthma, who was not immunosuppressed, was admitted for septic shock and disseminated intravascular coagulation (DIC) on the third day that she had varicella. She died two days after admission. A 43-year-old man with asthma, immunosuppressed because of systemic corticotherapy, was admitted for pneumonia, septic shock and DIC on the third day that he had varicella; he died the day after admission. A 41-year-old woman with leukemia, who was immunosuppressed, was admitted for pneumonia and septic shock on the first day that she had varicella; she died 20 days after admission. An 84-year-old man with heart failure was admitted for cellulitis and pneumonia on the second day that he had varicella; he died 48 days after admission. A 25-year-old man, in the terminal phase of Hodgkin's lymphoma, was admitted for pneumonia on the eighth day that he had varicella; he died the day after admission.

The death rate was 2.6/100,000 cases for the overall population, 0.5/100,000 for birth to 19-year olds, and 111.4/100,000 for people aged 20 years and older.

Analysis of costs associated with hospitalizations related to varicella: The treatment of varicella or its complications required 4280 hospitalization days, 74.9% of which were among people aged 18 years and younger. Moreover, 60.2% of all hospitalization days were for healthy people, compared with 26.5% for people with immunosuppression and 13.3% for people with a health problem other than immunosuppression.

The average cost for the type of hospitalization by health condition can be found in Table 5. The average NIRRU for all varicella hospitalizations was 0.889 (range 0.172 to 11.761). The average cost of a hospitalization was $2,504 and the total cost for all hospitalizations in both years was $2,276,136. The average cost of hospitalization was $2,336 (range $483 to $17,252) for a child and $3,159 (range $544 to $33,132) for an adult.

Healthy children represented 50.5% of all hospitalization costs. Although the average cost of hospitalization for an immunosuppressed child ($3347) was much higher than a child in good health ($2177), the overall cost of hospitalizing immunosuppressed children was only 13.5% of all costs.

DISCUSSION

The goal of the present study was to quantify varicella-associated morbidity in Quebec. By looking only at hospitalized cases, we were unable to obtain a complete picture of general morbidity associated with varicella. In addition, it is possible that some hospitalizations were incorrectly coded, and thus overlooked by our reviewers. Furthermore, because the study was limited to two years, it was difficult to evaluate accurately the mortality or incidence of congenital varicella, both very rare events. However, by validating all hospitalizations directly through hospital records, we were able to calculate the risk of severe complications precisely.

In Quebec, varicella causes about 450 hospitalizations every year, of which 80% are among children. Although morbidity is often associated with varicella in adults and immunosuppressed children, almost 60% of all hospitalizations were

for healthy children; these hospitalizations represented half of the costs.

The complication rates calculated by Choo et al (2) were five to six times higher than our rates, because Choo looked at all complications, whether or not the patient was hospitalized. The overall hospitalization rate calculated using our data (46.6 hospitalizations/10,000 cases, data not shown) is, however, comparable with that obtained by Choo et al (2) (43/10,000). Hospitalization rates by age group are also comparable, except among adults whose hospitalization rate in our study was almost four times higher than the rate found by Choo et al (2) (487.5 versus 125/10,000 cases).

Hospital costs obtained with the NIRRU were higher than the costs that we would have obtained had we used the method based on the cost of a one-day hospitalization in an acute care hospital (per diem). With this last method, the cost of an average stay (4.7 days), based on the 1995 per diem of $379 (9), would have been $1,781, and total hospitalization costs would have been $1,605,065, compared with $2,817 and $2,276,420, respectively, in our study.

However, the difference is much less than that observed between our cost calculation and the one reported by Law et al (10). In Law's study, the cost of hospitalizing a child with varicella complicated with a minor skin infection is estimated at $5,060 compared with $2,104 in our study. The finding that costs were calculated based on a daily hospitalization rate of $978 in tertiary care paediatric hospitals may explain the difference (11).

We did not find any studies that compared or validated these two cost calculation methods. The method based on NIRRU is used more and more because it takes into account the use of resources and the severity of the disease for each hospitalization, among other reasons. Estimated costs should be closer to the real costs.

Although the general population perceives varicella as a benign childhood disease, it can be accompanied by severe complications. Morbidity associated with varicella is one of the elements that has to be considered when evaluating the usefulness of varicella vaccine.

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