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MAJOR ARTICLE

Leveraging Influenza Virus Surveillance From 2012 to 2015 to Characterize the Burden of Respiratory Syncytial Virus Disease in Canadian Adults ≥50 Years of Age Hospitalized With Acute Respiratory Illness

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Background. Respiratory syncytial virus (RSV) disease in older adults is undercharacterized. To help inform future immunization policies, this study aimed to describe the disease burden in Canadian adults aged ≥50 years hospitalized with RSV.

Methods. Using administrative data and nasopharyngeal swabs collected from active surveillance among adults aged ≥50 years hospitalized with an acute respiratory illness (ARI) during the 2012–2013, 2013–2014, and 2014–2015 influenza seasons, RSV was identified using a respiratory virus multiplex polymerase chain reaction test to describe the associated disease burden, incidence, and healthcare costs.

Results. Of 7797 patients tested, 371 (4.8%) were RSV positive (2.2% RSV-A and 2.6% RSV-B). RSV prevalence varied by season from 4.2% to 6.2%. Respiratory virus coinfection was observed in 11.6% (43/371) of RSV cases, with influenza A being the most common. RSV hospitalization rates varied between seasons and increased with age, from 8–12 per 100 000 population in adults aged 50–59 years to 174–487 per 100 000 in adults aged ≥80 years. The median age of RSV cases was 74.9 years, 63.7% were female, and 98.1% of cases had ≥1 comorbidity. Among RSV cases, the mean length of hospital stay was 10.6 days, 13.7% were admitted to the intensive care unit, 6.4% required mechanical ventilation, and 6.1% died. The mean cost per RSV case was $13 602 (Canadian dollars) but varied by age and Canadian province.

Conclusions. This study adds to the growing literature on adult RSV burden by showing considerable morbidity, mortality, and healthcare costs in hospitalized adults aged ≥50 years with ARIs such as influenza.

Keywords. adult; burden; Canada; hospitalization; RSV.

Lower respiratory tract infections (RTIs) are the leading communicable cause of death globally, and like influenza virus, human respiratory syncytial virus (RSV) plays a major role [1–7]. RSV is a member of the Pneumoviridae family, and 2 subgroups (RSV-A and RSV-B) co-circulate annually with a seasonality similar to influenza virus in North America [8]. Like influenza virus, RSV is an important cause of respiratory disease in all age groups, but the burden of illness is greatest at the extremes of life [1–9]. In children <5 years of age, RSV is the most common cause of acute lower RTIs (eg, bronchiolitis) worldwide and is the leading cause of hospitalization for children <1 year of age in Canada and the United States (US) [1–9]. Most children are infected by RSV by the age of 2 years,

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and reinfections occur throughout life [9]. In healthy young adults, RSV infection typically ranges from asymptomatic to mild upper RTIs. However, RSV has been associated with excess mortality and hospitalization in older or other vulnerable adults [1–9]. With clinical trials pursuing RSV vaccines, new monoclonal antibodies, and RSV-specific antivirals in risk groups such as older adults, there has been renewed interest in characterizing the burden of adult RSV disease in Canada [8, 9].

The demonstrated efficacy of several new RSV vaccines in older adults means that decisions will need to be made about immunization programs. For this reason, prospective RSV surveillance in hospitalized adults was identified as a key priority by the Public Health Agency of Canada in order to characterize the burden of RSV disease in this age group [9]. The Canadian Immunization Research Network (CIRN) Serious Outcomes Surveillance (SOS) Network has been conducting prospective surveillance for acute respiratory illness (ARI) in hospitalized Canadian adults since 2009 [10] to evaluate vaccine effectiveness and characterize disease burden associated with respiratory pathogens like influenza virus [10–19], *Streptococcus pneumoniae* [20–24], severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [25], and RSV [26]. Leveraging CIRN SOS ARI surveillance data and specimens prospectively collected during the 2012–2013, 2013–2014, and 2014–2015 influenza seasons, this study characterized the burden of RSV disease in Canadian adults ≥50 years of age hospitalized with ARI.

METHODS

CIRN SOS Respiratory Virus Surveillance

The CIRN SOS Network initially captured information on adults ≥16 years of age [10], but adults aged ≥50 years were investigated in this study to characterize the burden of RSV disease in older adults. Adults admitted to hospital with ARI included individuals with any of the following: pneumonia, acute exacerbation of asthma or chronic obstructive pulmonary disease (COPD), unexplained sepsis, or any RTI or influenza-like symptom (eg, dyspnea, cough, sore throat, myalgia, arthralgia, fever, delirium/altered level of consciousness, and congestive heart failure). Following consent, detailed demographic information, surgical history, medical comorbidities, details of hospital care, complications, and outcomes were collected by interview and/or medical record review. Influenza seasons were considered from 15 November to 15 May for the years 2012–2013, 2013–2014, and 2014–2015. Nasopharyngeal (NP) swabs in universal transport media (Copan Diagnostics, Murrieta, California) prospectively collected for influenza virus detection were retrieved from −80°C archives and tested for RSV and other respiratory viruses. Patient demographics, signs and symptoms, and outcomes were classified by ARI cohorts representing cases of RSV, influenza A, influenza B, 1 of the other respiratory viruses detected in the multiplex polymerase chain reaction (PCR) assay, or patients who tested negative for respiratory viruses.

Respiratory Virus Multiplex Reverse-Transcription PCR

Two hundred microliters of specimen was subjected to a Total Nucleic Acid Isolation kit (Roche Diagnostics GmbH, Mannheim, Germany) on a MagNA Pure LC 2.0 instrument, followed by a 50-µL elution. From this, 10 µL was used as template for each of the 3 reactions of the Seeplex RV15 One-Step ACE Detection Assay (Seegene Inc, Seoul, Republic of Korea), as recommended by the manufacturer [17]. This assay detects and discriminates RSV-A and RSV-B as well as 13 other respiratory viruses. Amplicons from the multiplex reverse-transcription PCR (RT-PCR) were resolved using 1.2% (w/v) agarose gel electrophoresis with 1 µg/mL ethidium bromide staining. The prevalence of RSV, RSV-A, and RSV-B was determined by season, sex, and age.

Hospitalization Rates by Age

In a post hoc analysis, rates of hospitalization attributed to RSV were estimated as previously described for pneumococcal disease [23] by applying the CIRN SOS proportion of RSV ARI hospitalizations to the ratio of adults hospitalized with ARI obtained from Discharge Abstract Database (DAD) data of the Canadian Institute for Health Information (CIHI) (https://www.cihi.ca/en) and the annual Canadian population obtained from census data from Statistics Canada. Hospitalizations due to ARIs during the influenza seasons by month/year, by age-stratified groups (50–59, 60–69, 70–79, ≥80 years), or by specific age groups of interest (50–64, ≥50, ≥60, and ≥65 years) were provided by CIHI as anonymous and aggregate data using J12–J18 codes from the *International Classification of Diseases, 10th Revision* (*ICD-10*) with Canadian Enhancements. Incidence was expressed as estimates per 100 000 persons with 95% confidence intervals (CIs) for each of these age groups.

Resource Utilization

Methods used for calculating resource utilization were previously described by CIRN SOS for influenza illness [14]. Physician service fees and hospital costs were obtained from the Ontario Schedule of Benefits and the Hamilton Health Sciences, respectively. Ward per-diem costs included expenses for mechanical ventilation, supplemental oxygen, and procedures conducted at the bedside (eg, intubation). Laboratory tests, diagnostics, and imaging costs were provided separately. Costs for antimicrobials used during hospitalization were based upon unit prices provided by the Nova Scotia Health formulary, in which pharmacy human resources and supply acquisition costs were included. Costs of outpatient antimicrobials were based upon unit prices listed by the Ontario Drug Benefit formulary, with dosing consistent with the lowest

recommended dose according to product monographs for severe lower RTIs. Cost estimates were reported in Canadian dollars (CAD) by age and for each participating Canadian province.

Statistical Analysis

Statistical analyses were performed using SAS software, version 9.4 or later (SAS Institute, Cary North Carolina), and a *P* value ≤.05 was considered statistically significant. The *t* test and analysis of variance were used for comparing continuous variables, and χ^2 test was used to compare categorical variables. To identify patient and illness characteristics associated with death, multivariate analyses were performed using linear regression models with backward selection. Potential predictor variables were those found to be significantly associated with death in bivariate analyses as well as those previously identified as associated in other studies.

RESULTS

Proportion of RSV in Hospitalized Adults With ARI

Of 7797 tests performed, RSV was detected in 371 (4.8%) (Supplementary Table 1). Coinfection with another respiratory virus was observed in 43 of 371 (11.6%) RSV cases, with influenza A and B, rhinoviruses, and seasonal coronaviruses being the most common (Supplementary Table 2). Overall RSV prevalence varied little between seasons, from 4.2% (in 2013–2014) to 6.2% (in 2014–2015) (Supplementary Table 1). RSV prevalence was lowest in adults aged 50–59 years at 4.1% and highest in adults 60–69 years at 5.7%, and was equivalent for adults aged 70–79 and ≥80 years (4.6%). RSV prevalence was higher in females at 5.8% than in males at 3.6% (Supplementary Table 1). Over all seasons, RSV-A and RSV-B co-circulated with varying prevalence in each season (RSV-A, 2.0%–2.7%; RSV-B, 1.8%–4.3%) (Supplementary Table 1). Of RSV cases, the contribution of RSV-A was more common (60.9%) in the 2012–2013 season. RSV-A (47.5%) and RSV-B (53.2%) were nearly equally distributed in 2013–2014, and RSV-B (69.2%) was more common in 2014–2015.

Seasonal Estimates of RSV Hospitalization Rates

The seasonal incidence of hospitalization due to RSV increased with age in all seasons, with rates per 100 000 hospitalizations ranging from 8.2 to 11.8 for adults 50–59 years of age, 36.7 to 51.1 for those 60–69 years, 66.4 to 105.4 for adults 70–79 years, and 173.9 to 487.4 for adults ≥80 years (Table 1). Estimates of incidence for RSV-A and RSV-B are provided in Supplementary Table 3.

Patient Demographics

The median age of RSV cases was 74.9 years, very similar to that of infections due to other respiratory viruses (Table 2). Females were overrepresented among RSV cases at 63.7%, unlike the other cohorts where cases were almost equally distributed among males and females (Table 2). Adults with RSV and influenza infections were less likely to have a history of smoking than those with other respiratory viruses or patients in whom viral respiratory testing was negative. A higher proportion of RSV (8.8%), influenza A (9.1%), and influenza B (11.1%) cases were admitted from long-term care, compared to those with other respiratory viruses or patients in whom viral respiratory testing was negative. Influenza immunization rates were higher in RSV cases (67.7%), other viral cases (69.5%), and individuals testing negative for respiratory viruses (66.6%) compared to influenza A (58.5%) or B (59.6%) cases. Consistent with all cohorts, 26.8% of RSV cases had immunocompromising conditions, and almost all RSV cases (98.1%) had at least 1 comorbidity (Table 2). Like other respiratory viruses including influenza, the most common comorbidities in RSV cases were vascular, cardiac, pulmonary, renal, and endocrine (eg, complicated diabetes mellitus) (Table 2).

Table 1. Estimated Respiratory Syncytial Virus Hospitalization Rates Among Canadian Adults Aged ≥50 Years

Virus	Age Group, y	Seasonal Incidence Rates per 100 000 Population (95% CI)[a]			
		2012–2013	2013–2014	2014–2015	2012–2015
RSV (total)	50–59	9.3 (3.3–15.3)	11.8 (6.6–16.9)	8.2 (4.2–12.1)	13.9 (9.9–17.9)
	60–69	46.6 (30.9–62.4)	36.7 (25.6–47.8)	51.1 (29.8–72.5)	43.7 (34.2–51.2)
	70–79	105.4 (70.8–140.0)	66.4 (50.0–87.9)	103.7 (63.8–143.6)	88.6 (71.0–106.1)
	≥80	254.0 (179.9–328.1)	173.9 (124.9–222.9)	487.4 (369.3–605.5)	282.5 (238.2–326.8)
	50–64	32.0 (20.3–43.8)	27.3 (18.7–35.9)	28.1 (17.0–37.5)	33.6 (26.9–40.3)
	≥50	63.9 (52.6–75.1)	47.2 (39.5–54.8)	54.5 (62.3–88.4)	64.8 (58.4–71.1)
	≥65	80.7 (64.5–96.9)	57.0 (46.3–67.7)	68.6 (83.2–123.6)	80.8 (71.7–89.9)
	≥60	101.6 (91.0–112.2)	105.5 (86.2–124.8)	73.1 (60.4–85.8)	145.5 (118.7–172.4)

Abbreviations: CI, confidence interval; RSV, respiratory syncytial virus.

[a]For incidence calculations for age groups, the proportion of RSV attributed to community-acquired pneumonia by the Canadian Immunization Research Network's Serious Outcomes Surveillance Network from November to May of each year was applied to census data during this period, and the seasonal proportions of individuals hospitalized with an acute respiratory infection from Canadian Institute for Health Information Discharge Abstract Database data (excluding the provinces of British Columbia and Québec).

Table 2. Demographic Characteristics of Adults Hospitalized With Acute Respiratory Illness

Variable	RSV (n = 328)	FluA (n = 2155)	FluB (n = 606)	Other Respiratory Viruses (n = 596)	Negative for Respiratory Viruses (n = 3900)	*P* Value
Age, y, median (IQR)	74.9 (65–85)	75.9 (66–86)	76.2 (66–86)	74.7 (65–85)	74.0 (65–83)	<.001
Age category, y						
50–59	11.6 (38/328)	13.4 (289/2155)	12.7 (77/606)	12.9 (77/596)	14.1 (550/3900)	<.001
60–64	12.5 (41/328)	8.4 (180/2155)	8.4 (51/606)	10.6 (63/596)	10.3 (400/3900)	
65– 69	11.9 (39/328)	10.1 (218/2155)	11.1 (67/606)	11.2 (67/596)	11.1 (431/3900)	
70–79	24.4 (80/328)	23.6 (509/2155)	20.5 (124/606)	26.3 (157/596)	27.6 (1076/3900)	
≥80	39.6 (130/328)	44.5 (959/2155)	47.4 (287/606)	38.9 (232/596)	37.0 (1443/3900)	
Sex, male	36.3 (119/328)	48.7 (1050/2155)	44.1 (267/606)	45.5 (271/596)	48.5 (1893/3900)	<.001
Past or current smoker	54.4 (174/320)	52.5 (1103/2098)	44.2 (259/586)	62.8 (367/584)	68.7 (2633/3833)	<.001
BMI, kg/m^2, median (IQR)	26.4 (22.2–31.9)	25.9 (22.8–30.1)	25.9 (22.1–30.0)	26.0 (22.2–30.5)	25.8 (21.9–30.7)	.156
BMI category (kg/m^2)						
Underweight (<18.5)	6.2 (19/306)	4.6 (89/1929)	7.2 (38/525)	6.3 (36/567)	8.1 (297/3296)	<.001
Normal weight (18.5–24.9)	36.3 (111/306)	37.2 (718/1929)	37.5 (197/525)	36.7 (208/567)	36.9 (1348/3296)	
Overweight (25.0–29.9)	26.5 (81/306)	32.5 (626/1929)	30.1 (158/525)	29.3 (166/567)	27.1 (992/3296)	
Obese (30.0–40.0)	22.5 (69/306)	22.5 (434/1929)	20.4 (107/525)	22.6 (128/567)	22.1 (807/3296)	
Very obese (>40.0)	8.5 (26/306)	3.2 (62/1929)	4.8 (25/525)	5.1 (29/567)	5.7 (210/3296)	
Admitted from LTC	8.8 (29/328)	9.1 (195/2152)	11.1 (67/604)	7.7 (46/595)	7.6 (295/3895)	.028
Influenza immunization	67.7 (212/313)	58.5 (1197/2046)	59.6 (359/602)	69.5 (397/571)	66.6 (2484/3729)	<.001
Immunocompromise	26.8 (88/328)	27.2 (586/2155)	28.7 (174/606)	29.2 (174/596)	27.3 (1065/3900)	.817
≥1 comorbidity	98.1 (322/328)	94.7 (2040/2155)	94.5 (573/606)	98.0 (583/595)	95.9 (3739/3900)	<.001
Vascular	71.3 (234/328)	71.2 (1534/2155)	71.8 (435/606)	69.8 (416/596)	68.7 (2678/3900)	.212
Cardiac	55.5 (182/328)	46.4 (999/2155)	45.2 (274/606)	51.8 (309/596)	51.5 (2009/3900)	<.001
Pulmonary	48.2 (158/328)	38.3 (826/2155)	30.4 (184/606)	46.3 (276/596)	55.2 (2154/3900)	<.001
Renal	48.2 (158/328)	38.3 (826/2155)	30.4 (184/606)	46.3 (276/596)	55.2 (2154/3900)	.510
Endocrine	33.2 (109/328)	34.6 (746/2155)	31.7 (192/606)	31.3 (186/595)	30.8 (1200/3900)	.109
Diabetes mellitus, uncomplicated	6.4 (21/328)	5.2 (112/2155)	5.3 (32/606)	4.0 (24/595)	5.0 (194/3900)	
Diabetes mellitus, complicated	25.0 (82/328)	29.4 (634/2155)	26.4 (160/606)	27.2 (162/595)	25.8 (1006/3900)	
Neuromuscular	7.0 (23/328)	9.1 (197/2155)	10.1 (61/606)	8.2 (49/596)	6.8 (266/3900)	.004
Rheumatologic	3.7 (12/328)	4.3 (93/2155)	3.8 (23/606)	4.2 (25/596)	4.1 (160/3900)	.968
Gastrointestinal	2.1 (7/328)	3.1 (66/2155)	3.5 (21/606)	1.2 (7/596)	1.9 (76/3900)	.151
Hepatic	0.9 (3/328)	1.8 (38/2155)	1.6 (16/606)	2.0 (12/596)	1.7 (67/3900)	.379
Other chronic illnesses	12.2 (40/328)	19.4 (417/2155)	20.8 (126/606)	13.8 (82/596)	13.0 (508/3900)	<.001
No. of medications prior to admission						
0–4	19.0 (62/326)	28.8 (614/2134)	30.0 (179/596)	20.8 (122/587)	22.5 (870/3872)	<.001
5–7	30.1 (98/326)	28.7 (612/2134)	27.9 (166/596)	27.3 (160/587)	24.6 (951/3872)	
8–10	22.7 (74/326)	23.2 (495/2134)	23.8 (142/596)	27.3 (160/587)	23.6 (913/3872)	
11–13	13.8 (45/326)	10.8 (231/2134)	10.1 (60/596)	11.4 (67/587)	15.0 (580/3872)	
14–16	8.3 (27/326)	5.5 (118/2134)	5.4 (32/596)	8.3 (49/587)	8.5 (328/3872)	
>16	6.1 (20/326)	3.0 (64/2134)	2.9 (17/596)	4.9 (29/587)	5.9 (230/3872)	

Data are presented as % (no./No.) unless otherwise indicated. Coinfections were excluded to compare patient demographics between viruses.

Abbreviations: BMI, body mass index; FluA, influenza A; FluB, influenza B; IQR, interquartile range; LTC, long-term care; RSV, respiratory syncytial virus.

Presenting Signs and Symptoms

On admission, signs and symptoms for RSV cases were nonspecific and similar to those of other respiratory viruses (Supplementary Table 4). However, cough, difficulty breathing/shortness of breath, sputum production, wheeze, feverishness, runny nose/congestion, crackles, sore throat, chest pain, prostration, and stiff neck were more common in RSV than influenza, while measured fever (≥38°C), weakness, lethargy/malaise, myalgia, altered level of consciousness, muscle aches, and gastrointestinal symptoms were more common in influenza than RSV infections.

Clinical Outcomes

With few exceptions, the clinical outcomes of RSV-associated hospitalizations in adults were like those of influenza viruses (Table 3). At admission, RSV cases were more likely than influenza A cases to require oxygen therapy and to receive antibiotics prior to or during hospital admission. No significant

Table 3. Admission History, Clinical Course, and Outcomes of Adults Hospitalized With Acute Respiratory Illness

Characteristic	RSV (n = 328)	FluA (n = 2155)	FluB (n = 606)	Other Respiratory Viruses (n = 596)	Negative for Respiratory Viruses (n = 3900)	*P* Value
Admission history						
Antibiotic prior to admission	14.0 (46/328)	9.4 (203/2155)	12.7 (77/606)	8.2 (49/596)	8.9 (347/3900)	.001
Antibiotic during admission	88.7 (291/328)	85.8 (1850/2155)	82.8 (502/606)	91.1 (543/596)	86.8 (3385/3900)	<.001
Physician visit prior to admission	24.7 (81/324)	24.9 (537/2146)	32.2 (195/603)	22.9 (136/586)	20.1 (785/3842)	<.001
ED visit prior to admission	11.9 (39/325)	9.5 (205/2150)	10.9 (66/603)	8.2 (49/586)	9.5 (372/3861)	.366
Oxygen therapy during admission	75.3 (247/327)	65.2 (1405/2148)	57.1 (346/603)	72.8 (433/594)	71.4 (2786/3882)	<.001
Hospital LOS						
LOS, d, mean (range)	10.6 (1–74)	10.4 (1–162)	9.9 (1–132)	11.5 (1–102)	10.9 (1–163)	.100
LOS, d, median (IQR)	8 (5–12)	7 (4–11)	6 (4–11)	7 (5–12)	7 (5–12)	
ICU admission	13.7 (45/328)	13.2 (285/2155)	10.7 (65/606)	11.1 (66/595)	13.1 (511/3900)	.308
ICU days, mean (range)	9.2 (1–53)	10.2 (1–122)	10.4 (1–37)	9.9 (1–64)	8.3 (1–124)	.220
ICU days, median (IQR)	5 (3–9)	6 (3–10)	8 (4–14)	6 (3–11)	6 (3–10)	
Requirement of mechanical ventilation	6.4 (21/328)	7.7 (165/2155)	6.4 (39/606)	5.4 (252/595)	6.5 (509/3900)	.260
Mechanical ventilation days, mean (range)	10.6 (1–47)	11.2 (1–122)	10.9 (1–44)	10.7 (1–57)	8.7 (1–93)	.3555
Mechanical ventilation days, median (IQR)	5 (3–13)	6 (3–14)	8 (4–15)	6 (4–13)	5 (3–10)	
Mortality, day 30	6.1 (20/328)	8.7 (188/2155)	9.1 (55/606)	7.2 (43/596)	9.3 (668/3900)	.196
≥1 complication in hospital	50.3 (165/328)	69.9 (1505/2153)	66.1 (399/604)	53.5 (317/592)	53.8 (2094/3889)	<.001
Exacerbation of chronic disease	28.5 (47/165)	35.0 (527/1505)	27.6 (110/399)	28.7 (91/317)	36.1 (756/2094)	.001
New arrhythmia	10.3 (17/165)	11.1 (167/1505)	12.8 (51/399)	6.9 (22/317)	7.8 (163/2094)	.001
Sepsis	6.7 (11/165)	6.1 (92/1505)	6.0 (24/399)	4.1 (13/317)	7.2 (151/2094)	.260
Myocardial infarction	3.0 (5/165)	5.8 (88/1505)	5.5 (22/399)	2.8 (9/317)	3.0 (62/2094)	<.001
Nosocomial pneumonia	1.8 (3/165)	1.8 (27/1505)	1.3 (5/399)	1.6 (6/317)	1.3 (27/2094)	.772
ARDS	1.8 (3/165)	3.3 (50/1505)	2.3 (9/399)	1.6 (5/317)	2.2 (47/2094)	.191
DVT/pulmonary embolism	2.4 (4/165)	1.0 (15/1505)	0.3 (1/399)	0.6 (2/317)	1.4 (30/2094)	.105
Clostridioides difficile colitis	1.8 (3/165)	1.2 (18/1505)	2.5 (10/399)	1.9 (6/317)	1.2 (25/2094)	.244
Acute renal failure requiring dialysis	1.2 (2/165)	1.6 (24/1505)	2.3 (9/399)	0.6 (2/317)	1.7 (35/2094)	.526
Unstable angina	0.0 (0/165)	0.3 (5/1505)	0.5 (2/399)	0.0 (0/317)	0.3 (6/2094)	.716
Fracture	0.0 (0/165)	0.7 (11/1505)	1.3 (5/399)	2.5 (8/317)	0.6 (13/2094)	.005
Clinical outcome at discharge						
Died during admission	3.7 (12/328)	7.1 0(153/2155)	7.6 (46/606)	5.4 (32/596)	6.2 (243/3900)	<.001
Discharged home	80.2 (263/328)	82.0 (1767/2155)	83.7 (507/606)	76.7 (457/596)	78.3 (3054/3900)	
Discharged to LTC	5.2 (17/328)	2.0 (44/2155)	2.0 (12/606)	6.2 (37/596)	5.9 (230/3900)	
Discharged to assisted living	4.0 (13/328)	2.2 (47/2155)	1.0 (6/606)	5.0 (30/596)	2.9 (113/3900)	
Discharged to palliative care	0.6 (2/328)	0.3 (6/2155)	0.2 (1/606)	0.7 (4/596)	0.5 (18/3900)	
Transferred to a rehabilitation facility	2.7 (9/328)	3.2 (68/2155)	2.8 (17/606)	2.3 (14/596)	2.7 (106/3900)	
Transferred to another healthcare facility for completion of treatment	1.5 (5/328)	1.2 (25/2155)	0.7 (4/606)	1.2 (7/596)	1.6 (61/3900)	
Transferred to another healthcare facility for management of sequelae	0.9 (3/328)	0.4 (9/2155)	0.5 (3/606)	0.5 (3/596)	0.5 (21/3900)	
In hospital, alternate level of care	0.9 (3/328)	1.2 (26/2155)	0.8 (5/606)	1.0 (6/596)	1.1 (41/3900)	
Recovered but in hospital, unrelated	0.3 (1/328)	0.1 (3/2155)	0.0 (0/606)	0.2 (1/596)	0.1 (4/3900)	

Data are presented as % (no./No.) unless otherwise indicated. Coinfections were excluded to compare patient outcomes between viruses.

Abbreviations: ARDS, acute respiratory distress syndrome; DVT, deep vein thrombosis; ED, emergency department; FluA, influenza A; FluB, influenza B; ICU, intensive care unit; IQR, interquartile range; LOS, length of stay; LTC, long-term care; RSV, respiratory syncytial virus.

differences were observed between RSV and influenza cases for mean length of hospital stay (LOS). However, RSV cases had the highest median LOS (8 days). Of the RSV cases, 13.7% required intensive care unit (ICU) admission and 6.4% required mechanical ventilation, similar to influenza. Mortality at 30 days in RSV cases was 6.1% compared to 8.7% in influenza A and 9.1% in influenza B. RSV cases were less likely than influenza cases to have complications, but when they occurred, the complications were like those seen with influenza. As seen with the other pathogens or those without any pathogens, most RSV cases (80.2%) were discharged home. However, a higher proportion of RSV cases were discharged to long-term care (5.2%), assisted living (4.0%), or palliative care (0.6%), or transferred to another healthcare facility for completion of treatment (1.5%) or for management of sequelae (0.9%) compared to influenza cases (Table 3). When the 43 RSV cases coinfected

with other respiratory viruses were included, there was a trend toward more serious outcomes with the increased proportions of individuals requiring mechanical ventilation and mortality both at 7.0% (Supplementary Table 5). In a multivariable regression analysis model, adults aged ≥75 years with RSV were more likely to succumb to their illness than RSV-negative comparators in the same age group (Supplementary Table 6).

Healthcare Utilization

The mean cost per RSV hospitalization was $13 602 (CAD) (Table 4). The lowest cost was in adults aged 50–59 years at $9340, while it was the highest in adults aged 65–69 years ($19 786). Cost per RSV case varied between provinces, with New Brunswick being the lowest at $7862 and Québec the highest at $20 291.

DISCUSSION

The burden of RSV disease was characterized in Canadian adults ≥50 years of age hospitalized with ARI during the 2012–2013, 2013–2014, and 2014–2015 influenza seasons using archived NP swabs and patient data previously recorded for influenza surveillance. RSV contributed to 4.8% of adults hospitalized with ARI, and both RSV-A and RSV-B co-circulated with altering proportions between seasons. RSV incidence increased with age and caused significant morbidity and mortality, and the cost per RSV case was similar to that previously reported for influenza cases [14]. These data are important, as characterizing the RSV disease burden in adults is a key priority to inform immunization policy for forthcoming RSV immunization programs [8, 9].

Table 4. Estimated Costs per Polymerase Chain Reaction–Confirmed Respiratory Syncytial Virus Hospitalization

Variable	Mean Cost, CAD (95% CI)
Age, y	
50–59 (n = 44)	$9340 ($6218–$12 461)
60–64 (n = 43)	$14 207 ($8651–$19 763)
65–69 (n = 47)	$19 786 ($9845–$29 727)
70–79 (n = 92)	$13 052 ($9037–$17 067)
≥80 (n = 145)	$13 060 ($10 087–$16 033)
Province[a]	
Alberta (n = 3)	$9280 ($1894–$16 665)
British Columbia (n = 16)	$11 763 ($9034–$14 493)
New Brunswick (n = 20)	$7862 ($5812–$9913)
Nova Scotia (n = 19)	$13 204 ($9213–$171 194)
Ontario (n = 274)	$13 260 ($10 700–$15 821)
Québec (n = 38)	$20 291 ($11 513–$29 068)
Overall (n = 371)	$13 602 ($11 481–$15 723)

Abbreviations: CAD, Canadian dollars; CI, confidence interval.

[a]Manitoba only reported 1 respiratory syncytial virus case; therefore, no cost was presented.

Of 7797 adults hospitalized with ARI, RSV was detected in 4.8%, but this proportion varied between seasons from 4.2% to 6.2%. This is consistent with previous Canadian studies involving adults hospitalized with ARI, and those of other countries [1, 5–7, 26–34]. Another Canadian study in the same population showed a lower annual proportion (2%–3%) of ARI attributed to RSV [27], but the use of administrative databases was expected to underestimate RSV disease due to undertesting in routine clinical care [8, 30]. Interestingly, the current study did not observe an increase in RSV prevalence with age as reported by others [4–6]. In a recent CIRN study [26], RSV prevalence in hospitalized adults 50–64, 65–79, and ≥80 years was 5.3%, 6.4%, and 7.1%, respectively. In this study, RSV prevalence increased from 4.1% in adults 50–59 years of age to 5.7% in those 60–69 years of age, but this trend did not continue in older adults despite higher volume of testing in older adults. As seen with SARS-CoV-2, it is possible that upper respiratory tract sampling (ie, NP swab collections) may not always adequately detect RSV disease that has progressed to the lower RTI. Previous studies described the benefits of adding a lower respiratory tract specimen (ie, sputum) to upper tract collections, leading to increased RSV prevalence from 1.6% to 4.6% [6]. Another possibility is that NP swabs might be less likely to be collected from frail older adults whose goals of care may not support aggressive pursuit of ARI etiology, as has been observed in vulnerable older adults hospitalized with influenza or pneumococcal disease [22–25].

Despite the possible underestimation of RSV in older adults, the proportion of ARI attributed to RSV was used to estimate RSV hospitalization rates as a post hoc analysis. As expected, RSV hospitalization rates increased with age among adults ≥50 years, and rates were higher than anticipated [5, 6, 27, 30]. In a previous Canadian study using administrative data [27], the annual incidence of RSV hospitalizations per 100 000 population ranged between 1 and 30 for adults 50–64 years and between 10 and 100 in adults ≥65 years, and was >100 per 100 000 for adults aged ≥80 years. For the same age groups, this study showed higher seasonal rates per 100 000 between 27.3 and 32.0 for adults 50–64 years, 57.0 and 80.7 for adults ≥65 years, and 173.9 and 487.4 for adults ≥80 years. These values are consistent with those described in some other countries [1]. Seasonal RSV incidence per 100 000 population in hospitalized US adults was significantly higher, ranging from 33.5–63.0 for adults 50–64 years to 136.9–255.6 for adults ≥65 years of age [31]. In a recent systematic review and meta-analysis of RSV disease burden in adults ≥60 years in high-income countries [1], the RSV hospitalization rate per 100 000 individuals was 145 (95% CI, 94–224), which is similar to the rates in similarly aged adults observed in this study of 101.6 (95% CI, 91.0–112.2) for all years. Apart from the possible underestimates of RSV prevalence in older adults mentioned earlier, RSV hospitalization rates were likely also underestimated with use of CIHI

DAD data, which only represent approximately 75% of Canadian hospitalizations due to the absence of data from British Columbia and Québec, and the *ICD-10* codes did not capture all possible contributors to ARI. It would be of interest to further characterize the burden of RSV in Canadian adults at risk for serious outcomes (eg, chronic medical conditions like COPD or immunosuppression) [26], as incidence was shown to increase several-fold in these populations [5, 6, 31]. Most adults hospitalized with RSV in this study had risk factors for serious outcomes. RSV cases were mostly older adults (ie, median age, 74.9 years), 98.1% had ≥1 underlying medical comorbidity, 54.4% had a history of smoking, 57.5% were either overweight or obese, and 26.8% were immunocompromised. Sex was not equally distributed in RSV cases, with females representing 63.6%. In the literature, females are more likely to seek care for respiratory symptoms, but male sex has been identified as a risk factor for severe RSV infection and hospitalization [6].

The clinical outcomes observed for RSV were similar to those of influenza A and B viruses in this study and previous studies by the CIRN SOS Network [10–20, 26]. A greater proportion of RSV cases required noninvasive ventilation at 75.3% compared to 65.2% and 57.1% for influenza A and B, respectively. RSV showed a median LOS of 8 days (vs 7 and 6 days for influenza A and B, respectively), 13.7% of RSV-positive patients were admitted to ICU (vs 13.2% and 10.7%), the mean number of ICU days was 9.2 days for RSV cases (vs 10.2 and 10.4 days), the need for mechanical ventilation was 6.4% in RSV cases (vs 7.7% and 6.4%), and mortality at 30 days was 6.1% (vs 8.7% and 9.1%). Relatively similar outcomes were reported for RSV by other studies, with minor variations attributed to differences in populations with risk factors for serious outcomes [26, 31–40]. In a recent systematic review and meta-analysis, the in-hospital case fatality rate in high-income countries was 7.15% (95% CI, 5.40%–9.36%), which is comparable to the current study [1]. Interestingly, when the 43 RSV cases co-infected with other respiratory viruses in the current study were analyzed compared to RSV cases alone, a relatively higher proportion of individuals required mechanical ventilation (7.0%) and mortality was higher (7.0%) when RSV cases were coinfected (Supplementary Table 5). This was consistent with previous studies in hospitalized adults coinfected with RSV and influenza [40]. Future research could consider stratifying clinical outcomes by other risk factors for serious RSV disease, such as older age, chronic medical conditions, or an overall frailty-based stratification [12, 19, 25].

RSV hospitalization is a significant driver of healthcare costs. The costs associated with RSV infection varied by age ($13 052–$19 786) and province ($7862–$20 291), but the mean costs per case was $13 602. This is almost identical to the mean cost of influenza in hospitalized adults at $14,612, with provincial variations between $13 711 and $20 808 [14]. Using currency conversion factor (1 US dollar [USD] = 1.37117 CAD) to compare studies, the mean cost per RSV cases in hospitalized US adults was similar at $11 522 CAD ($8403 USD) [34]. Predictors for higher costs included ICU admission and hospital LOS, which are similar in this study [34]. In the US, the annual cost of RSV hospitalizations in adults ≥50 years of age was estimated at >$1 billion dollars [34]. If the cost per RSV case and RSV hospitalization rates in the current study are applied to Canadian census data, the cost of RSV hospitalization during influenza seasons alone in adults ≥50 and ≥60 years of age would be more than $71 million and $65 million CAD, respectively. This estimate seems consistent with those of the US, given that Canada represents approximately 10% of the US population. It should also be noted that in a recent Canadian study, the average healthcare cost per RSV case in hospitalized adults aged 50–64 years was $19 586 CAD when assessed at 30 days following diagnosis but increased to $80 408 by day 365 [7]. When comparing the cost per RSV hospitalization at 30 versus 365 days for adults 65–79 years and for adults ≥80 years, similar increases were observed from $17 507 to $96 271 and from $13 746 to $71 773, respectively [7]. Like the current study, Rafferty et al [7] also showed there was an increase in RSV hospitalization costs from adults 50–59, 60–64, and 65–69 years of age, but the cost did not further increase for older Canadian adults of 70–79 or ≥80 years. It could be speculated that in older adults, the higher mortality may contribute to the reduced cost of hospitalization; however, explanations are likely multifactorial. Compared to influenza [14], the current study showed that RSV cases required a higher level of care at discharge for ongoing management of treatment, complications, or sequelae. These costs were not captured in the current study and would be anticipated to accrue over time. RSV infections in vulnerable adults ≥50 years of age were shown to lead to long-term impacts on productivity, emotional functioning, and social activities [35], functional decline following hospital discharge in those ≥60 years [36], and increased requirements for additional care in older adults in general [37]; mortality within a year was almost 33% in seniors aged ≥75 years [38]. Of note, a multivariable regression analysis model in the current study demonstrated that adults ≥75 years with RSV were more likely to die from their illness than RSV-negative comparators in the same age group (Supplementary Table 6). Future studies should consider long-term follow-up of RSV cases including costs incurred to better assess the true impact of RSV infection in adults. Consideration should also be given for comparison between the pre– and post–coronavirus disease 2019 (COVID-19) pandemic timelines, as the delivery of care models might have changed during the COVID-19 pandemic [39]. Unfortunately to date, no funding has become available to the CIRN SOS Network to support ongoing surveillance of RSV hospitalizations in Canada. To capture the full burden of RSV disease in Canada, RSV should be considered as a

reportable disease in each Canadian province and territory, and more in-depth surveillance could leverage existing infrastructures such as those of the CIRN SOS Network for hospitalized adults, and others to capture pediatric hospitalizations and community-based respiratory disease surveillance for all age groups [9, 41–43].

As discussed above, the major limitations of this study are its time frame, the seasonality of surveillance, and potentially an underrepresentation of RSV with use of a conventional RT-PCR (ie, RV15) rather than real-time RT-PCR known to be more sensitive for the detection of respiratory viruses [44–46]. More recent studies are also warranted, particularly with the reemergence of RSV following relaxation or removal of public health mitigation strategies implemented during the COVID-19 pandemic [39]. Although RSV and influenza seasons generally overlap, starting surveillance at the beginning of influenza circulation will tend to miss the beginning of RSV circulation. As such, this study did not aim to fully capture the numerical burden of RSV among hospitalized patients with ARI, but rather to investigate outcomes and costs. This limitation could be mitigated by current COVID-19–inspired efforts to conduct surveillance on a year-round basis. Nonetheless, this study adds to the much-sought growing literature on adult RSV disease by showing considerable morbidity, mortality, and healthcare costs in hospitalized adults ≥50 years, as seen with influenza virus. This helps understand the burden of RSV disease in hospitalized Canadian adults, which in turn helps inform and direct immunization policy for forthcoming RSV immunization programs.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author contributions. J. J. L. and M. E. were involved in the writing of the original draft. J. J. L., S. A. M., M. E., D. M.-C., M.-P. D., O. G., and J.-Y. P. were involved in the conceptualization and methodology. L. Y., D. M.-C., M. E., and J. J. L. were involved in data curation and formal analysis, M. E., A. A., J. M. L., and J. J. L. were involved in supervision, and all authors were involved in project administration, investigation, writing, review, and editing. All authors approved the final version of the manuscript.

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Patient consent. Approval was sought from local research ethics boards (REBs) at IWK (REB 1024817) and Nova Scotia Health (REB 1024818) before supplemental testing and secondary use of the Canadian Immunization Research Network (CIRN) Serious Outcomes Surveillance (SOS) Network data. Unique study identifiers enabled laboratory results to be linked to previously collected patient demographic and clinical outcome data. Written informed consent was obtained at the time of enrollment for each patient at each hospital site in accordance with REB policies and included future testing for other respiratory pathogens (ClinicalTrials.gov identifier NCT01517191). The protocol was approved by the REB of all participating institutions, and the full names of individual REBs are as follows: Nova Scotia Health REB (Halifax site); Mount Sinai Hospital REB (Mount Sinai and Toronto Invasive Bacterial Diseases Network sites); Hamilton Health Sciences/McMaster Health Sciences REB (Hamilton site); the University of British Columbia Clinical REB (Vancouver site); Ottawa Health Science Network REB (Ottawa site); Comité d'éthique de la recherche du Centre hospitalier universitaire de Québec (Québec City site); Comité d'éthique de la recherche sur l'humain du Centre Hospitalier Universitaire de Sherbrooke (Sherbrooke site); Horizon Health Network REB (Saint John site); Montreal General Hospital Research Ethics Committee (Montreal site); North York General REB (North York site); Toronto East General Hospital REB (Toronto East site); William Osler Health System REB (William Osler site); and Health Sciences North REB (Sudbury site).

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