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Seasonal Incidence of Medically Attended Respiratory Syncytial Virus Infection From 2015 to 2019 in a Cohort of Adults With High-risk Conditions

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Background. Adults with high-risk conditions (underlying health conditions that increase risk of severe outcomes after respiratory infection) may have a substantial incidence of respiratory syncytial virus (RSV), but existing information on this topic is limited. We assessed the seasonal incidence of RSV in adults with high-risk conditions in a Wisconsin community.

Methods. We conducted a retrospective study using data and respiratory specimens from participants with medically attended acute respiratory illness (MAARI) in a test-negative study of influenza vaccine effectiveness. We included individuals ≥18 years old in 2015–16 through 2019–20 seasons, with ≥1 high-risk condition. Residual respiratory specimens were retested for RSV using a multiplex viral panel. We calculated seasonal incidence using Poisson regression and population weighting, with the sum of observed and extrapolated RSV cases in the study cohort divided by the number of adults with high-risk conditions in the underlying source population.

Results. Of 3601 respiratory samples tested, 97% were White and 66% were female. The mean (standard deviation) age of participants was 53 (19) years. We identified 303 RSV infections; 40% were RSV A. Estimated incidence of RSV-related MAARI was 94.1 (79.5–111.5) per 10 000 high-risk adults across all seasons and varied by season. Age-specific incidence per 10 000 was 69.3 (95% confidence interval [CI], 52.4–91.7) for those 18–49 years; 131.6 (95% CI, 92.3–187.6) for those 50–59 years; 109.9 (95% CI, 80.2–150.6) for those 60–74 years; and 150.5 (95% CI, 100.8–224.6) for those ≥75 years.

Conclusions. Overall, these findings suggest a substantial incidence of RSV-related MAARI in adults with high-risk conditions.

Keywords. adults; community burden; high risk; incidence; medically attended; RSV; viral epidemiology.

Respiratory syncytial virus (RSV) causes a substantial proportion of respiratory illnesses in young children [1] and older adults [2, 3]. However, a growing body of evidence suggests that adults of all ages with certain underlying health conditions, also known as "high-risk conditions," may also experience a substantial burden of RSV [2]. Examples of such high-risk conditions include chronic obstructive pulmonary disease (COPD), asthma, heart failure, diabetes, and immunosuppressive disorders [2, 4]. Several studies have highlighted the need for more evidence on the burden of RSV infection and the risk of severe RSV infection in adults with high-risk conditions [5, 6]. However, there are challenges in identifying RSV infection in adults because it usually presents as a nonspecific illness ranging from cold-like symptoms to severe respiratory distress that could be a result of a wide spectrum of viral respiratory pathogens [7]. It is likely that RSV infection is underdiagnosed in adults because the clinical presentation of RSV infection in adults can resemble illnesses caused by other respiratory viruses, the length of illness, and duration of viral shedding of RSV is reduced in adults compared to children (meaning that specific tests for RSV may fail to identify cases when RSV was present), and RSV testing is not routinely conducted in the outpatient setting, likely in part because of a lack of RSV-specific treatments available for this age group [8], leading to potential underestimation of RSV incidence and burden. It may be additionally possible that cases of RSV are missed due to the type of sample collected or type of testing performed to identify RSV [9].

Population-based studies of RSV in adults with high-risk conditions are needed for vaccine recommendations and planning, future predictive modeling of seasonal RSV epidemics, and estimating RSV-associated healthcare resource utilization. We assessed RSV seasonal cumulative incidence in adults aged

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≥18 years with high-risk conditions, using existing respiratory specimens collected from Marshfield Clinic Health System (MCHS) enrollees of an influenza vaccine effectiveness study, from 2015–16 through 2019–20 winter respiratory virus seasons [10].

METHODS

Adults With High-risk Conditions

Participants of MCHS Flu VE studies were included in this analysis if they were aged ≥18 years, participated in the Flu VE study in at least 1 respiratory season from 2015–16 through 2019–20, and had at least 1 underlying health condition that was considered to increase their risk of severe illness after RSV infection (at least 1 "high-risk condition"). Exact dates of seasons are available in Supplementary Table 1.

High-risk conditions were defined by having at least 1 applicable International Classification of Diseases (ICD) code documented in the participant's electronic health record during specific time frames relative to an index date of September 1 preceding the start of the winter respiratory season of enrollment and ranging from the past 6 months to ever, depending on the condition (Supplementary Tables 2 and 3). High-risk conditions were grouped into the following categories: cardiac disorders (arrhythmias, heart failure, and coronary artery disease), chronic respiratory diseases (COPD, asthma, and cystic fibrosis), chronic liver disease, chronic kidney disease, diabetes, and immunocompromised status (transplant, malignancy, current treatment with immunosuppressive medication, and other immunosuppressive disorders). "Malignancy" included the following: lymphomas, multiple myeloma and malignant plasma cell neoplasms, leukemias, and other and unspecified malignant neoplasms of lymphoid, hematopoietic, and related tissue.

Underlying Source Population

The source population for the Flu VE study is established before the beginning of each winter respiratory virus season. The source population included (1) residents of the Marshfield Epidemiologic Study Area (MESA), a defined geographic area of 14 ZIP codes that includes Marshfield, Wisconsin (WI) and surrounding area, for ≥12 months or since birth [11] and (2) individuals seen at MCHS medical facilities in Marshfield, Colby/Abbotsford, Wausau, or Weston, WI. Individuals who were not MESA residents were required to have at least 2 encounters in the past 3 years within MCHS, on 2 different dates, with 1 of the encounters being with a provider type of doctor of medicine, doctor of osteopathy, nurse practitioner, physician assistant, or resident at a recruitment facility.

Flu VE Enrollment Visit

Throughout the influenza season, individuals who were members of the source population who had a medically attended acute respiratory illness (MAARI) in an outpatient setting were systematically recruited by study staff. Individuals were eligible to participate in the Flu VE study if they were aged ≥6 months, had an acute respiratory illness with cough, illness duration ≤7 days, and had not taken an influenza antiviral medication in the past 7 days. Individuals could be enrolled more than once per influenza season if their previous enrollment occurred ≥14 days prior. Enrollment of individuals was triggered by 2 consecutive weeks of increasing detection of influenza by real-time reverse transcriptase polymerase chain reaction conducted as part of preenrollment surveillance, and ceased when at least 1 week was observed with no influenza detections among subjects enrolled in the study (or, as long as possible based on funding, if influenza activity did not cease after 10 weeks). For the current analysis, only adults ≥18 years with high-risk conditions enrolled in the Flu VE study and from the source population were included.

Data and Specimen Source

At the time of enrollment in the Flu VE study, participants completed an enrollment questionnaire and authorized access to electronic health records to collect additional relevant information. The enrollment questionnaire obtained information on race/ethnicity; education level; self-reported general health before their illness (a 5-point Likert scale, where 1 = excellent, 2 = very good, 3 = good, 4 = fair, and 5 = poor); symptom onset date; and symptoms and signs (fever/feverishness, fatigue/feeling run down, nasal congestion, wheezing, shortness of breath, sore throat, muscle pain/myalgia, headache, and/or vomiting). Information extracted from the electronic health record for this secondary analysis included: high-risk conditions (as described previously); sex; and Charlson comorbidity index score.

Participants provided a respiratory specimen (combined nasal and throat swabs) for influenza testing. Residual specimens were archived after testing. For the current analysis, archived specimens were retested for the presence of RSV A and B via a multiplex assay, the GenMark ePlex Respiratory Pathogen Panel, according to manufacturer specifications and recommendations, with appropriate quality controls [12].

Statistical Methods

We estimated the seasonal incidence of medically attended RSV cases per 10 000 adults with high-risk conditions, for any RSV infection and by RSV type (A and B), using stratification and weighting methods similar to those used in previous estimates of RSV incidence [13, 14]. Specifically, we used data on adults with high-risk conditions within the Flu VE study and within the Flu VE source population. The populations of adults with high-risk conditions in the Flu VE study and source population were stratified into mutually exclusive groups based on age category (a; 18–49, 50–59, 60–74, and ≥75 years), an individual's number of MAARI visits (m) during a given study enrollment

period, sex (g), MESA residency status (r), and season (s). Weighting for the number of MAARI visits (m) was account for the proportion of individuals who may seek care more often by including as a weighting stratum the number of MAARI that an individual has in a year.

A sampling weight was calculated for each individual in the high-risk Flu VE study population per (a, m, g, r, s) stratum (Supplementary Table 4). This sampling weight was equivalent to the ratio of the number of adults with high-risk conditions in the source population in a given (a, m, g, r, s) stratum, to the number of adults with high-risk conditions in the Flu VE study population in that stratum. We used these sampling weights to estimate the total number of medically attended RSV infections in each stratum among adults with high-risk conditions in the source population.

We also used RSV surveillance data provided by the Wisconsin State Laboratory of Hygiene (WSLH) RSV surveillance data to further weight our incidence estimates for a standard 31-week time period each winter (Centers for Disease Control and Prevention week 40 through week 18 the following calendar year) [15, 16]. This was necessary to account for the shorter enrollment intervals compared to the longer seasonal intervals when RSV was circulating in the community. For each season, we multiplied the sampling weights by a ratio defined as the total number of WSLH RSV-positive counts divided by the sum of WSLH RSV-positive counts occurring during the shorter enrollment interval.

We used Poisson regression with defined analytic weights as described previously, offsets and robust variance estimation [17, 18] to estimate seasonal incidence with corresponding 95% confidence intervals (CI), and to perform statistical tests comparing subgroups by winter respiratory virus season, age, sex, and RSV type. We calculated the numerator as the number of RSV cases in the Flu VE study population and then estimated the number of cases in the source population. Offset terms were stratified by winter respiratory virus season, age group, number of MAARI visits, and sex. Acknowledging that high-risk condition categories may vary substantially by age, cumulative incidence estimates were also calculated by high-risk condition within age categories. Each offset was the natural log of the number of cohort members in a stratum divided by the total sum of analytic (numerator) weights. Incidence estimations were based on 2 key assumptions: first, test results from enrolled patients with MAARI could be extrapolated to the non-enrolled source population, based on the number of MAARI visits per season; and second, RSV cases occurring outside the enrollment period for the Flu VE study were proportional to RSV cases identified by the WSLH during that time period.

Patient Consent Statement

The MCHS institutional review board reviewed and approved this study with a waiver of informed consent. Patients provided consent before participating in the original Flu VE study.

RESULTS

Descriptive Characteristics

There were 3604 respiratory samples from the Flu VE study from eligible adults with high-risk conditions for this analysis; 3601 samples were successfully retested (the remaining 3 samples could not be tested because of low volume or poor quality). Among the 3601 samples, 303 (8.4%) were positive for RSV. The highest proportion of individuals testing positive for RSV occurred in the 2017–18 season, when 83 of 867 individuals (9.6%) tested positive (Figure 1). Among all participants, 52% had ≥2 high-risk conditions in separate condition categories (58% in those with RSV). There was a higher proportion of adults 18–49 years of age among individuals with non-RSV MAARI compared to individuals with RSV MAARI; a higher proportion of individuals with RSV MAARI reported nasal congestion, wheezing, and shortness of breath associated with their illness. Conversely, fever/feverishness was more common among non-RSV MAARI. A statistically significant higher proportion of individuals with RSV MAARI had underlying coronary artery disease; higher proportions of individuals with RSV MAARI were also observed among individuals with COPD and individuals with transplant, though these were not statistically significant. Additional demographic and illness characteristics of adults with and without RSV are reported in Table 1. Among RSV-positive adults, demographic and illness characteristics were similar for RSV A compared to RSV B cases (Supplementary Table 5). Estimates were similar when restricting calculations to be based on individuals living in MESA Central only (Supplementary Table 6).

Seasonal Incidence

Among adults with high-risk conditions, estimated seasonal incidence of RSV-associated outpatient MAARI was 94.1 (95% CI, 79.5–111.5) per 10 000 (Table 2). Seasonal incidence was 38.6 (95% CI, 29.2–50.9) per 10 000 for RSV A and 56.0 (95% CI, 45.4–69.1) per 10 000 for RSV B. Results were similar in a sensitivity analysis restricted to individuals residing in MESA Central only (data not shown).

RSV incidence varied by season, from 78.9 (95% CI, 53.5–116.4) per 10 000 high-risk adults in 2015–16 to 112.1 (95% CI, 81.6–154.2) per 10 000 in 2018–19. Although both RSV A and RSV B were identified in each season, incidence estimates suggested that either RSV A or RSV B tended to be predominant in any individual season; the 2016–17 and 2019–20 seasons appeared to be RSV A–dominant seasons, whereas RSV B appeared to be predominant in 2015–16, 2017–18, and 2018–19. Estimated seasonal incidence was 69.3 (95% CI, 52.4–91.7) per 10 000 high-risk adults aged 18–49 years; 131.6 (95% CI, 92.3–187.6) per 10 000 high-risk adults aged 50–59 years; 109.9 (95% CI, 80.2–150.6) per 10 000 high-risk adults aged 60–74 years; and 150.5 (95% CI, 100.8–224.6) per 10 000 high-risk adults aged ≥75 years. Estimated seasonal

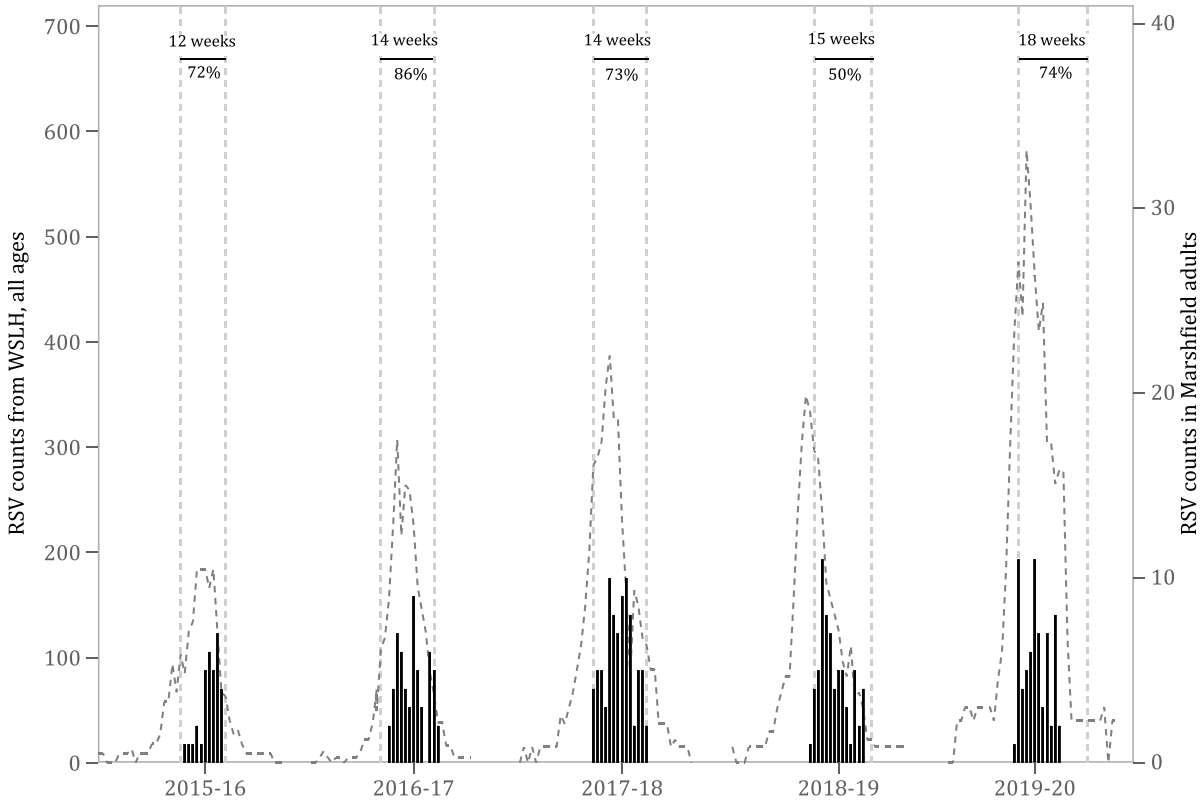

Figure 1. Medically attended RSV cases in high-risk Marshfield study participants ≥18 y old and statewide RSV counts (all ages) based on testing at the Wisconsin State Laboratory of Hygiene. Study enrollment periods are identified by vertical dashed lines; percent of all statewide cases occurring during each enrollment period is shown at top. Abbreviation: RSV, respiratory syncytial virus.

incidence of any RSV, RSV A, and RSV B by demographic characteristics and high-risk conditions are shown in Table 2 and in Figure 2. Although CIs for age-specific, high-risk condition-specific estimates were wide and did not differ statistically, point estimates appeared to generally be higher for older adults and for adults with heart failure (Figure 2).

DISCUSSION

Using data and samples prospectively collected from 5 respiratory virus seasons, we observed that RSV was a common cause of MAARI, occurring in 303 of 3601 (8%) outpatient respiratory illness ambulatory care visits, where respiratory samples were collected and tested. Our findings are similar to a previous prospective community cohort study that identified similar incidence estimates of RSV in adults with high-risk conditions (physician-diagnosed congestive heart failure or chronic pulmonary disease), with RSV infection reported in 4%–10% of high-risk adults [2].

Several other studies have investigated RSV in individuals with specific high-risk conditions. In a prospective cohort study in adults with cystic fibrosis, approximately 2% of samples tested positive for RSV [19]. A separate community cohort study of adults with primary antibody deficiency reported an estimated annual RSV incidence as 0.8% [20]. In a single-season prospective cohort study of 62 individuals who had received a bone marrow or stem cell transplant, there were 53 episodes of respiratory illness reported among 35 individuals; 2 specimens tested positive for RSV [21]. In a similar single-season prospective cohort of 50 individuals who had received a lung transplant, there were 49 episodes of respiratory illness among 32 individuals; 8 individuals tested positive for RSV [22]. Finally, a medical record–based study of lung transplant recipients from 1996–2000 found that of 21 individuals with community-acquired respiratory viral infection, 8 cases were attributable to RSV [23].

Our findings are similar to estimates from our own previous work in older adults (including individuals with and without high-risk conditions). Our previous work identified an incidence of 124 RSV cases per 10 000 adults aged 50–59 years [13], compared to an estimate of 132 per 10 000 high-risk adults in this study. Similarly, our previous work identified an incidence of 139 RSV cases per 10 000 adults aged ≥60 years [24], whereas the current study identified an incidence of 110 RSV cases (95% CI, 80–151) per 10 000 high-risk adults aged 60–74, and 150 RSV cases (95% CI, 101–225) per 10 000 high-risk adults aged ≥75 years.

Table 1. Demographic Characteristics of Adult Cohort Members With High-risk Conditions by RSV Status, 2015–16 Through 2019–20

	RSV MAARI[a]		Non-RSV MAARI[a]		*P* Value
	n = 303	%	n = 3298	%	
RSV season: n (%)					.41
2015–16	33	10.9	458	13.9	
2016–17	55	18.2	640	19.4	
2017–18	83	27.4	784	23.8	
2018–19	65	21.5	657	19.9	
2019–20	67	22.1	759	23.0	
Age group, n (%)					< .01
18–49 y	90	29.7	1367	41.4	
50–59 y	58	19.1	639	19.4	
60–74 y	84	27.7	842	25.5	
≥75 y	71	23.4	450	13.6	
Female sex: n (%)	199	65.7	2159	65.5	.94
Race/ethnicity: n (%)[b]					< .01
Black or African-American	2	0.7	16	0.5	
Asian	3	1.0	19	0.6	
Native Hawaiian or other Pacific Islander	1	0.3	1	0	
American Indian or Alaska Native	0	0	8	0.2	
Other (includes multiple races)	8	2.6	52	1.6	
White	289	95.4	3198	97.0	
Hispanic[c]	10	3.3	78	2.4	.12
Education level: n (%)[d]					.97
Less than high school graduate	25	8.3	249	7.6	
High school graduate or obtained an equivalent certification	108	35.6	1152	34.9	
Some college (including vocational training and/or associate's degree)	113	37.3	1298	39.4	
Bachelor's degree	34	11.2	378	11.5	
Advanced degree	22	7.3	214	6.5	
Illness signs and symptoms[e]: n (%)					
Fever/feverishness	168	55.4	2135	64.7	<.01
Fatigue/feeling run down	283	93.4	3082	93.5	.97
Nasal congestion	278	91.7	2684	81.4	<.01
Wheezing	227	74.9	1980	60.0	<.01
Shortness of breath/trouble breathing	222	73.3	2170	65.8	<.01
Sore throat	195	64.4	2223	67.4	.28
Muscle pain/myalgia	42	62.7	538	70.9	.16
Headache	48	71.6	586	77.2	.30
Vomiting	27	40.3	274	36.1	.49
Self-reported general health before illness: median (IQR)[f]	3.0 (2.0–3.0)		2.0 (2.0–3.0)		.51
Days from symptom onset to specimen collection: median (IQR)	4.0 (3.0–5.0)		3.0 (2.0–5.0)		.19
Charlson score: mean (SD)	1.5 (2.0)		1.1 (1.6)		<.01
Number of high-risk conditions in separate condition categories: median (IQR)[g]	2.0 (1.0–3.0)		2.0 (1.0–2.0)		.01
Number of high-risk conditions in separate condition categories: n (%)[g]					.04
1	128	42.2	1588	48.2	
2	79	26.1	914	27.7	
3	62	20.5	511	15.5	
≥4	34	11.2	285	8.6	
High-risk conditions: n (%)					
Any high-risk condition that is not immunocompromising	300	99.0	3275	99.3	.48
Any cardiac disorder	211	69.6	2259	68.5	.68
Heart failure	36	11.9	286	8.7	.06
Arrhythmias	192	63.4	2104	63.8	.88
Coronary artery disease	71	23.4	555	16.8	< .01
Any chronic respiratory condition	140	46.2	1428	43.3	.33
Asthma	90	29.7	1028	31.2	.60
COPD	68	22.4	573	17.4	.03
Cystic fibrosis	0	0	3	0.1	–

Table 1. Continued

	RSV MAARI[a]		Non-RSV MAARI[a]		*P* Value
	n = 303	%	n = 3298	%	
Chronic liver conditions	49	16.2	445	13.5	.19
Chronic kidney disorders	104	34.3	1005	30.5	.16
Diabetes	87	28.7	821	24.9	.16
Any immunocompromising condition	27	8.9	199	6.0	.05
Transplant	14	4.6	88	2.7	.05
Malignancy	16	5.3	130	3.9	.26
Immunosuppressive medications	0	0	12	0.4	–
Other immunodeficiencies	9	3.0	64	1.9	.22

Abbreviations: COPD, chronic obstructive pulmonary disease; IQR, interquartile range; MAARI, medically attended acute respiratory illness; RSV, respiratory syncytial virus; SD, standard deviation.

[a]RSV MAARI = participants with RSV-positive MAARI episode. Non–RSV-MAARI = participants with RSV-negative MAARI episode.

[b]Four RSV-negative individuals declined to provide information about their race or ethnicity.

[c]Individuals may have Hispanic ethnicity and any additional race listed; therefore, this category is not mutually exclusive from other categories listed.

[d]One RSV-positive and 7 RSV-negative individuals declined to provide information about their education status.

[e]Study participants were required to have cough to be eligible to participate. Therefore, cough is not reported among these symptoms. Muscle pain/myalgia, headache, and vomiting were assessed in the 2019–20 season only.

[f]Self-rated general health before illness was rated on a 5-point Likert scale, with 1 = poor, 2 = fair, 3 = good, 4 = very good, and 5 = excellent.

[g]Separate condition categories defined as: (1) chronic respiratory diseases, (2) chronic liver disease, (3) cardiac disorders, (4) chronic kidney disease, (5) diabetes, and (6) immunocompromised status. An individual would have a value of 1 if they had high-risk conditions that fell into only 1 of these categories. They would have a value of 2 if they had high-risk conditions that fell into 2 separate categories listed (for example, if they had high-risk conditions classifying them as having both a chronic respiratory disease and a chronic liver disease).

Table 2. Seasonal Incidence of RSV-associated Outpatient Medically Attended Acute Respiratory Infection in Adults With High-risk Conditions From 2015–16 Through 2019–20 Seasons

	Seasonal Incidence Per 10 000 High-risk Adults (95% CI)					
	RSV (All Subtypes)		RSV A		RSV B	
	Seasonal incidence[a,b]	95% CI	Seasonal incidence	95% CI	Seasonal incidence	95% CI
Overall	94.14	79.47–111.53	38.56	29.23–50.86	56.00	45.42–69.06
Season						
2015–16	78.90	53.51–116.36	26.31	13.51–51.25	52.59	32.37–85.44
2016–17	93.78	64.33–136.72	53.11	32.23–87.51	42.40	23.83–75.45
2017–18	97.13	70.65–133.54	12.57	5.11–30.90	84.56	60.58–118.05
2018–19	112.13	81.54–154.21	49.49	32.01–76.51	62.65	39.47–99.42
2019–20	83.34	55.49–125.19	58.83	34.04–101.68	24.51	15.87–37.87
Sex						
Female	90.75	74.03–111.24	28.75	20.76–39.80	62.58	48.79–80.27
Male	103.05	76.23–139.32	64.29	40.96–100.92	38.76	28.10–53.48
Age group						
18–49 y	69.31	52.36–91.74	30.49	20.08–46.28	39.58	27.46–57.04
50–59 y	131.61	92.32–187.64	48.46	27.50–85.39	83.15	51.99–132.98
60–74 y	109.89	80.20–150.57	44.06	24.68–78.68	65.83	45.98–94.23
60–64 y	153.05	98.98–236.66	80.44	40.31–160.55	72.61	43.28–121.83
65–69 y	93.33	47.37–183.87	32.08	8.19–125.65	61.24	28.68–130.77
70–74 y	81.22	51.56–127.96	20.32	9.11–45.35	60.90	35.43–104.70
≥75 y	150.46	100.78–224.62	56.38	24.34–130.63	94.07	61.39–144.15
75–79 y	139.98	73.21–267.64	59.01	19.13–182.06	80.97	34.53–189.83
≥80 y	139.58	91.38–213.22	47.29	16.32–137.01	92.30	62.10–137.18
High-risk conditions[c]						
Any condition that is not immunocompromising	93.59	78.90–111.01	38.61	29.24–50.98	55.40	44.84–68.44
Cardiac disorders[d]	94.07	77.06–114.83	40.67	29.04–56.97	54.02	42.68–68.38
Heart failure[e]	175.88	109.93–281.41	90.01	38.85–208.50	85.88	53.56–137.70
Arrhythmias[f]	92.61	75.41–113.75	39.06	27.63–55.22	54.22	42.41–69.32

Table 2. Continued

	Seasonal Incidence Per 10 000 High-risk Adults (95% CI)					
	RSV (All Subtypes)		RSV A		RSV B	
	Seasonal incidence[a,b]	95% CI	Seasonal incidence	95% CI	Seasonal incidence	95% CI
Coronary artery disease[g]	121.25	85.21–172.54	54.44	28.08–105.52	66.81	46.92–95.13
Chronic respiratory conditions[h]	96.12	77.01–119.95	33.06	23.89–45.75	63.05	47.77–83.23
Asthma[i]	87.38	67.06–113.86	31.43	20.99–47.06	55.95	40.57–77.15
COPD[j]	135.01	99.51–183.16	40.55	26.03–63.15	94.46	63.36–140.83
Cystic fibrosis[k]	–	–	–	–	–	–
Chronic liver conditions	107.54	71.46–161.86	48.74	26.90–88.32	58.80	34.35–100.65
Chronic kidney disorders	125.19	92.25–169.89	64.06	39.91–102.80	61.13	41.14–90.84
Diabetes	138.54	101.35–189.36	64.02	39.37–104.11	74.52	48.76–113.88
Any immunocompromising condition[l]	124.00	77.49–198.42	37.83	20.85–68.62	86.17	46.29–160.42
Malignancy[m]	136.87	70.07–267.36	23.63	9.30–60.01	113.24	51.87–247.24
Transplant[m]	104.51	57.08–191.34	51.33	26.38–99.86	53.18	19.69–143.64
Immunosuppressive medications[n]	–	–	–	–	–	–
Other immunodeficiencies	146.92	67.08–321.78	77.17	34.71–171.54	69.75	17.11–284.43

Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease; ICD, International Classification of Diseases; RSV, respiratory syncytial virus.

[a]Seasonal incidence calculated using a Poisson regression with a log link, sampling weights, offsets, and robust variance estimation. Adjustment factors are additionally applied based on the estimated true length of the RSV season, according to Wisconsin State Laboratory of Hygiene reports for each season. This adjustment factor is based on the inverse of the proportion of all statewide cases that occurred during seasonal enrollment periods. Wisconsin RSV cases were determined for the period week 40 through week 18, and for the specific study enrollment window each winter using data reported by the Wisconsin State Laboratory of Hygiene. CIs are Wald 95% CIs. Offset terms are stratified by winter respiratory virus season, age group, number of medically attended acute respiratory infection encounters per season, and sex. Each offset is the natural log of number of individuals in a sampling stratum divided by total sum of analytic weights in the stratum.

[b]Estimates generated by extrapolating the number of medically attended acute respiratory infections among adults in the high-risk adult cohort to the high-risk adult source population.

[c]Cardiac disorders, chronic respiratory conditions, chronic liver conditions, chronic kidney disorders, diabetes, and "immunocompromised" definitions are not mutually exclusive. For example, it is possible for an individual to have both a cardiac disorder and an immunocompromising condition. In the row titled "All nonimmunocompromised individuals (excluding individuals with an immunocompromising condition)," we exclude all individuals with an immunocompromising condition.

[d]Cardiac disorders is a group that includes several cardiac disorders, not limited to heart failure, coronary artery disease, and/or arrhythmia. For a full list of cardiac disorders included in this parent category, please refer to Supplementary Table 3.

[e]Heart failure is a subcategory of cardiac disorders. For a full list of defining ICD-10 codes, corresponding ICD-9 codes and relevant time frames, refer to Supplementary Table 3.

[f]Arrhythmias are a sub-category of cardiac disorders. For a full list of defining ICD-10 codes, corresponding ICD-9 codes and relevant time frames, refer to Supplementary Table 3.

[g]Coronary artery disease is a sub-category of cardiac disorders. For a full list of defining ICD-10 codes, corresponding ICD-9 codes and relevant time frames, refer to Supplementary Table 3.

[h]Chronic respiratory conditions is a group that includes several chronic respiratory conditions, not limited to COPD and/or asthma. For a full list of respiratory conditions included in this parent category, please refer to Supplementary Table 3.

[i]Asthma is a subcategory of chronic respiratory conditions. For a full list of defining ICD-10 codes, corresponding ICD-9 codes, and relevant time frames, please refer to Supplementary Table 3.

[j]COPD is a subcategory of chronic respiratory conditions. For a full list of ICD-10 codes, corresponding ICD-9 codes, and relevant time frames, please refer to Supplementary Table 3.

[k]There were no RSV-positive individuals with cystic fibrosis in this analysis.

[l]Immunocompromised individuals are any individuals with an immunocompromising condition as listed in Supplementary Table 3. Individuals with immunocompromising conditions may have other conditions that are not immunocompromising, such as asthma or COPD.

[m]"Transplant" includes ICD codes referring to "transplanted organ and tissue status" as well as "complications of transplanted organs and tissue." "Malignancy" includes ICD codes referring to lymphoma, leukemia, and multiple myeloma and malignant neoplasms. For further detail, please refer to Supplementary Tables 2 and 3.

[n]There were no RSV PCR-positive individuals receiving immunosuppressive medications in this analysis.

In a systematic review and meta-analysis, it was identified that estimates of RSV incidence may be higher in the outpatient setting compared to emergency department or hospital [9]. Meta-analytic findings have estimated 13 hospitalizations, 198 emergency department (ED) admissions, and 1401 outpatient visits per 100 000 US adults aged <50 years. These were lower than estimates in adults aged 65 years and older, which estimated 267 hospitalizations, 200 ED admissions, and 2278 outpatient visits per 100 000 US adults aged 65 years and older [9]. Other findings from a study conducting active surveillance for ambulatory care visits for ARI (similar to our study) found similar estimates of RSV incidence in adults (not restricted to adults with high-risk conditions) [25]. Our findings are complementary to a reported incidence rate of 13.2 RSV-related ED visits per 10 000 adults aged 18–49 years [26] (though that analysis assessed RSV-related ED visits throughout a 12-month period and did not restrict analysis to the winter respiratory virus season, when RSV is more common).

Results from our current analysis found a similar seasonal incidence of RSV in older adults with high-risk conditions versus results identified earlier in a population of older adults with and without high-risk conditions [13]. Similarly, our analysis yielded age category-specific incidence estimates with overlapping 95% CIs, for adults aged 50–59 years, 60–64 years, 65–69 years, and 70–74 years. Previous work has estimated a higher mean seasonal RSV-attributable general practitioner visits and hospitalization in high-risk older adults versus older adults without specific high-risk conditions [27]. The similarity

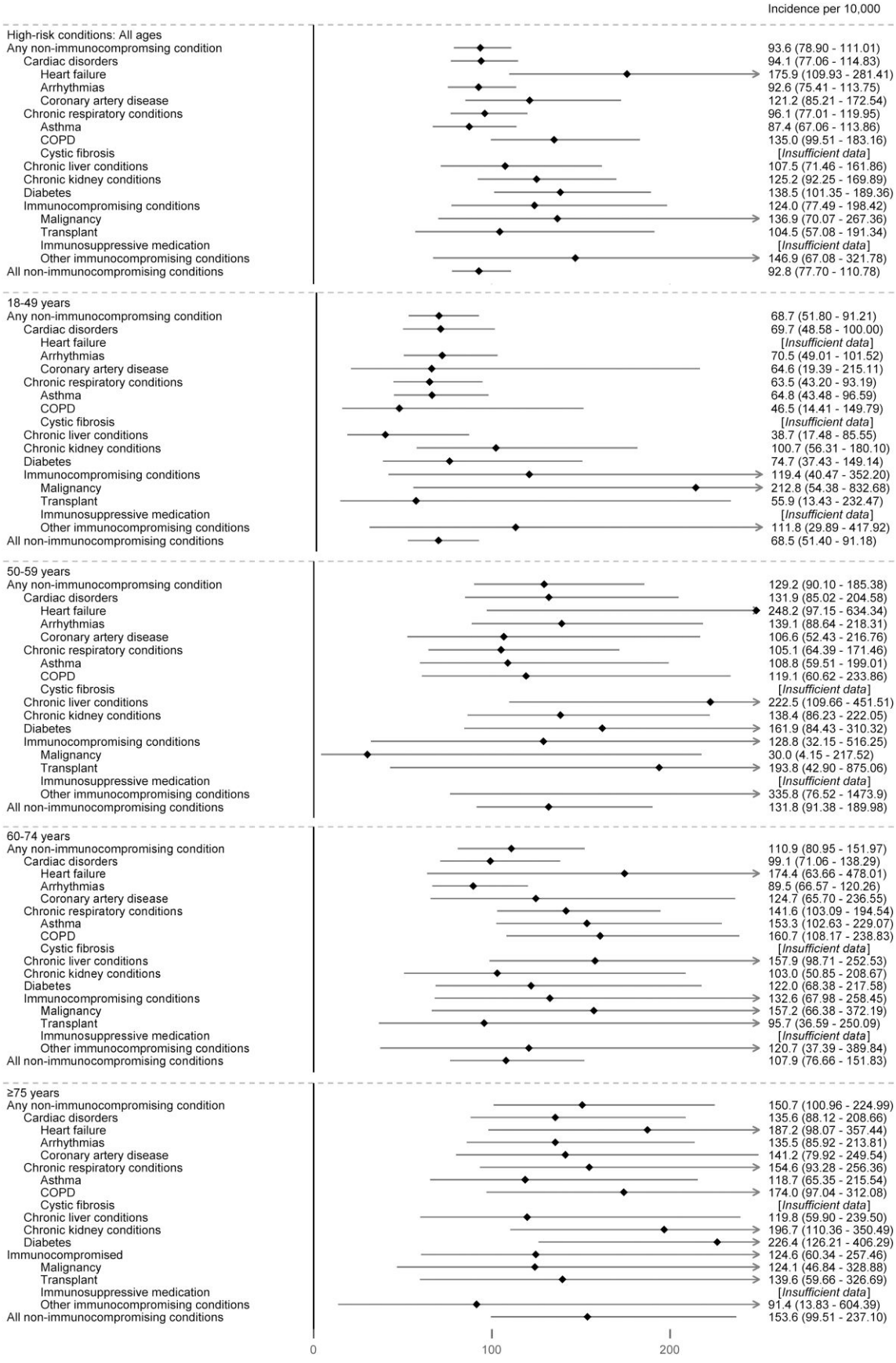

Figure 2. Cumulative incidence estimates for RSV by age and high-risk conditions. Abbreaviation: RSV, respiratory syncytial virus.

between these estimates in our study, compared to findings elsewhere, are likely from a combination of several factors. First, the comparator study did not exclude high-risk adults. Second, the proportion of older adults with high-risk conditions in the comparator study was high, meaning that the 2 groups may have been similar even though only 1 was restricted to individuals with high-risk conditions (the comparator study found that among RSV cases, 15% of individuals had COPD, 7% had congestive heart failure, 14% had asthma, 6% were immunocompromised, and 21% had diabetes). Third, a majority of individuals in this analysis were community-dwelling adults; the study did not emphasize enrolling older adults in congregate living settings such as skilled nursing facilities or assisted living who may have been more likely to have a higher proportion of severe outcomes after RSV infection. Despite these mitigating factors, results from this study suggest that future research is needed to further characterize the burden of RSV infection in high-risk adults and to inform future RSV vaccination recommendations.

Limitations

This analysis has several limitations. First, the analysis is based on a study originally designed to assess seasonal influenza circulation in outpatient settings. Because influenza and RSV may not always present with identical symptoms, and influenza and RSV seasons may not overlap perfectly; this could have resulted in systematically missing some RSV cases. We attempted to mitigate this by adjusting incidence estimates by WSLH-based estimates of RSV circulation. However, WSLH RSV information relies on voluntarily reported cases of RSV by clinicians and is likely to largely represent pediatric patients. Therefore, this adjustment is likely imperfect in the context of adult populations. Additionally, the underlying Flu VE study enrollment was restricted to outpatient settings, but adults with high-risk conditions may be more likely than otherwise healthy adults to seek care directly in the hospital or in the ED. Because Flu VE study enrollment did not occur in ED or inpatient settings, these individuals would have been missed in the study, potentially biasing study results toward identifying less severe cases of ARI. Finally, there exists the possibility that individuals determined to be ineligible for participation due to receipt of influenza antiviral medication could have had RSV. As those individuals were not eligible to participate in the study, we cannot independently verify their RSV status.

Similarly, we could not identify the etiology of illness for individuals who were excluded from Flu VE study eligibility for symptom duration >7 days. Although the distribution of days from symptom onset to respiratory sample collection was similar in individuals with and without RSV, it is challenging to verify the disease etiology in individuals with illness duration longer than 7 days. It is therefore possible that some individuals with illness duration >7 days would have otherwise tested positive for RSV as a Flu VE study enrollee. In the same vein, there is a body of literature suggesting that imperfect test sensitivity may result in an underdetection of RSV [9, 28–30]. Because this study relied on respiratory samples (nasal and throat) only to identify RSV, some cases of RSV may have been missed.

Our incidence calculations include a key assumption that RSV test results from enrolled Flu VE study participants can be extrapolated to nonenrolled individuals in the community who had a similar illness during the study enrollment period. Similar assumptions have been applied in other work calculating respiratory virus incidence [13, 14]. However, if nonenrolled individuals in the underlying source population were systematically different from enrolled Flu VE participants according to risk of medically attended RSV, our seasonal incidence calculations could either over- or underestimate the underlying incidence of medically attended RSV in the community.

This analysis identified wide CIs for some seasonal incidence estimates that were further stratified by age, sex, and certain high-risk conditions. This is a result of small numbers of individuals in certain strata, as well as epidemiological heterogeneity of RSV A and RSV B in different seasons. Therefore, stratified incidence estimates should be interpreted with caution. Additionally, the interpretation of these estimates should be considered alongside the fact that they are based on outpatient ARI visits only and did not include individuals going directly to the hospital or the ED for an acute respiratory illness. Therefore, the incidence estimates reported here are only 1 component of the total burden of RSV in this population.

This analysis contains information from a population dwelling in a rural community, where greater than 95% of the study participants identified as White. Although other studies have not identified a biological role in the relationship between race or ethnicity and risk of RSV infection directly [31, 32], analyses have acknowledged the role of discrimination on the basis of race in poor outcomes for RSV among Hispanic and American Indian/Alaska Native individuals [33] and Black individuals [34]. The findings from this population may therefore have limited external generalizability to more urban settings and to other populations.

Finally, this analysis identified different health conditions to represent "high-risk" status. Among adults with the same high-risk conditions, different individuals may have varying levels of severity of those conditions (for example, among individuals with asthma, some individuals may have well-controlled asthma and others may have poorly controlled asthma). This heterogeneity within specific high-risk groups may differentially impact the risk of medically attended RSV infection. Therefore, incidence estimates according to high-risk conditions should be interpreted with the acknowledgment that they represent underlying heterogeneity in individual health conditions.

CONCLUSIONS

Our analysis identified substantial incidence of RSV in adults 18 years and older with high-risk conditions over the course of 5 winter respiratory virus seasons. These findings support the continued surveillance and assessment of RSV, especially in younger adults with high-risk conditions. Additionally, continued epidemiological and clinical support may be needed for serious RSV illness, in high-risk and older-adult populations.

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

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