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Respiratory Syncytial Virus (RSV) Laboratory Surveillance and Mortality in Nebraska, 2016 – 2021

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Respiratory syncytial virus (RSV) laboratory surveillance and mortality in Nebraska, 2016 – 2021.

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Abstract

Respiratory syncytial virus (RSV) is a common respiratory virus affecting children and adults. The United States RSV peak season occurs regularly between October to May, but in April 2021, an unexpected United States interseason RSV epidemic ensued. RSV laboratory testing has changed in the United States due to increased use of nucleic acid amplification testing (NAAT) rather than antigen-based testing, affecting how RSV seasonal epidemics are determined. Nebraska linked RSV laboratory and death certificate data (2016-2021) were used to calculate crude, specific and adjusted RSV case and mortality rates by age, sex, race, and ethnicity. A Cochran – Armitage test for trend examined changes in RSV testing type across the surveillance period to determine Nebraska RSV test type changes compared to the United States. Very low RSV mortality across the surveillance period and high cases rates in 2020 and 2021. This is the first multiyear report of Nebraska RSV descriptive epidemiological trends during the COVID-19 pandemic.

Research Aims

Aim	Objective	Analysis
1	Clean and link Nebraska RSV surveillance laboratory reports to Nebraska death certificate reports (2016 – 2021).	Data quality checking and management in SAS. One-to-one and one-to-many exact match linkage. Comparison of frequency between native and linked surveillance and death certificate datasets.
2	Calculate, analyze, and visualize trends in Nebraska RSV surveillance laboratory reports and RSV-indicated mortality cases, 2016 – 2021. Calculate crude, specific, and directly standardized RSV annual case rate by age, sex, race, and ethnicity.	Calculated direct weight adjusted specific RSV case rates using Nebraska US Census standard populations. Crude rate calculation of RSV linked and non-linked mortality. Visualized with time trends, summary tables, and spatial RSV positivity rates.
3	Assess Nebraska RSV positivity, case rate, and mortality trend changes during the COVID-19 pandemic.	Before and during COVID-19 pandemic year comparison of RSV in Nebraska using calculated time trends and rates visualized as summary tables and epidemic curves.
4	Evaluate Nebraska RSV positivity trends by RSV test type and by Cochran – Armitage test for trend, 2016 – 2021.	SAS-executed Cochran-Armitage test for trend with frequency plot and statistical output tables.

<u>Background</u>

RSV is a common respiratory virus affecting children and adults, with young children (less than 2 years old) and older adults (greater than 65 years old) experiencing more severe morbidity and mortality at the poles of age (Schweitzer, et al., 2021). RSV is directly transmitted (person-to-person) via respiratory droplets and the incubation period range is 2 – 8 days with a mean incubation period of 4 – 6 days (Schweitzer, et al., 2021). Mild, uncomplicated RSV disease presents as an upper respiratory tract infection in healthy adults. Reinfection in those over 2 years old with no underlying immune condition is frequently observed in uncomplicated RSV illness (Schweitzer, et al., 2021). Most children are expected to have their first RSV infection by 2 years old (Brochers, et al., 2013).

In children younger than 2 years, especially between 0 – 6 months, the primary RSV infection more often exhibits severe disease as a lower respiratory tract infection with airway obstruction leading to wheezing (bronchiolitis) or other lung involvement (Schweitzer, et al., 2021). Extended contagious periods due to weakened host immune conditions can occur in RSV up to 4 weeks (Schweitzer, et al., 2021). Approximately 58,000 United States annual RSV hospitalizations are estimated to occur in children younger than 5 years old (Rha, et al., 2020). Approximately 5 – 10% of primary RSV childhood infections require hospitalization in the intensive care unit (Borchers, et al, 2013). Comorbid conditions with the greatest RSV morbidity and mortality include immunocompromised, premature infants, asthmatics, and chronic obstructive pulmonary disorder (Schweitzer, et al., 2021). Rarely, severe RSV disease can manifest as pneumonia, hospitalization, apnea, or death in young children and older adults (Brochers, et al., 2013). Approximately 14,000 United States RSV deaths are estimated to occur each year (Falsey, et al., 2005).

RSV is a single-stranded RNA virus from the *Paramyxoviridae* viral family (Crowe, et al., 2018). There are two RSV strains circulating in human populations, RSV – A and RSV-B. The strains are about 25% antigenically-related, which may partially explain the seasonal predominance of a single strain and persistent reinfection in human populations (Crowe, et al., 2018).

In the 1980s, the Centers for Disease Control and Prevention (CDC) established the National Respiratory and Enteric Virus Surveillance System (NREVSS) to track specific respiratory viruses like RSV via sentinel surveillance voluntary laboratory reporting (CDC, 2020). Specimen type, time and location of collection, and positivity rate are determined through NREVSS for every state in the US (CDC, 2020). Some Nebraska sentinel laboratories reporting to NREVSS are Chadron Community Hospital, Children's Hospital and Medical Center – Omaha, Morrill County Community Hospital, Nebraska Medicine, Offutt Air Force Base, and the Regional West Medical Center in Scottsbluff, showing rural and urban Nebraska coverage (CDC, 2021). Additionally, all electronically reporting laboratories in Nebraska must report RSV tests as positive or negative within 7 days from the test result per 173 Nebraska Administrative Code (NAC) 1-004.02. Non-electronic RSV laboratory reporting in Nebraska is voluntary. Logical, Observation, Identifiers, Names, and Codes (LOINC) is a standardized and universal coding system for indicating laboratory test information across health care systems ("What LOINC Is," n.d.). A LOINC code enables translation of a local laboratory test code to a standardized laboratory test code. ("What LOINC Is," n.d.).

Three RSV laboratory tests or assays types are available in the United States with varying practical advantages and disadvantages. Cell culture has been the standard for

respiratory virus detection due to its accuracy and potential for identifying viral coinfections (Henrickson, et al., 2007). However, cell culture requires specific expertise for specimen handling, long wait time (approximately 2 – 5 days), and high costs in production and labor compared to other RSV tests (Henrickson, et al., 2007). Antigen-based tests, specifically immunofluorescent (IF) antibody and enzyme-linked immunoassays (EIA), are highly sensitive and specific during RSV peak season with low expertise required for administering the test – a frequently-cited reason for these tests in outpatient settings (Henrickson, et al., 2007). Off-season RSV antigen-based tests may not be as sensitive or specific, limiting its utility. Nucleic acid amplification tests (NAAT) like polymerase chain reaction (PCR) tests are molecular-based tests that are more sensitive and specific than antigen-based tests and represent the new "gold standard" for RSV testing without seasonality requirements (Henrickson, et al., 2007). In terms of procedural expertise, NAAT can be sophisticated, but generally take less time to receive results compared to cell culture. Despite multiple test options, many providers forego RSV testing because it will unlikely affect clinical management due to the lack of effective RSV-specific treatment, historically contributing to under reporting of RSV positive cases (Falsey, et al., 2005).

RSV epidemic seasons are defined by the CDC as the onset of the first two-consecutive weeks when mean RSV antigen positivity is greater than 10%, or 3% for PCR tests (Midgley, et al., 2017). The consistent predictability of the RSV season onset has changed at the national level due to increasing preference for PCR testing in United States laboratories (Midgley, et al., 2017; Olsen, et al., 2021). In the United States, RSV seasonal epidemics occur annually in temperate areas between October and March (Crowe, et al., 2018). Seasonal RSV epidemics are consistent in the United States temperate areas while

tropical areas like Florida experience prolonged, attenuated RSV-infection trends or dual peaks in the spring and fall months (Borchers, et al., 2013; CDC, 2020).

On January 21, 2020, the first confirmed case of COVID-19 occurred in the United States in Washington State (AJMC, 2021). Due to rising confirmed cases of COVID-19 in the United States, subsequent public health and national emergencies were declared in March 2020, funding contact tracing and COVID-19 prevention efforts. Prevention messaging included staying at home, mask wearing, and social distancing (AJMC, 2021; Olsen, et al., 2021). Infectious respiratory diseases are diverse, but respiratory hygiene and standard precautions function with general effectiveness for any respiratory viruses (Houghton, et al., 2020). Herculean efforts to prevent widespread COVID-19 transmission in the United States led to reductions of other respiratory viruses beginning in approximately March 2020, including influenza virus, common non-COVID-19 coronaviruses, parainfluenza viruses, human metapneumovirus, RSV, and rhinoviruses despite an increase in PCR testing for all respiratory viruses in Spring 2020 (Olsen, et al., 2021).

Significance

Thacker describes how annual and archival surveillance reports can estimate magnitudes, monitor risk factor trends, identify changes in laboratory testing affecting epidemiological measures, and enable hypothesis testing research (Brownson, 2006, p. 37). Data linked between RSV surveillance positivity, annual case rates and mortality can enable trend analysis between RSV testing and mortality at the Nebraska level. Linked data analysis is a system thinking tool that can enable new insights from cross-discipline collaboration in public health outcomes. Trend changes at the national level for RSV laboratory testing and RSV season definitions have been reported, but prior to this study,

RSV laboratory reporting changes over multiple years in Nebraska had yet to be reported and evaluated (Olsen, et al. 2021). Improved understanding of RSV laboratory testing trends could lead to insight regarding demographic groups who are tested or not tested, changes occurring due to the COVID-19 pandemic, and Nebraska-specific laboratory testing and surveillance system capacity. Nebraska-level laboratory testing may be dissimilar to national level reporting, which could inform Nebraska-based providers for timely, cost-effective RSV testing in outpatient settings (Henrickson, et al., 2007). Surveillance reports generate hypotheses, where future studies can test further relationships uncovered in this report, including RSV risk factors by demographics, RSV natural history, and RSV testing accuracy and mortality outcomes.

Methods

Populations

The source population comprises RSV laboratory-tested individuals and RSV mortality cases reported to Nebraska. The sample population was any reported RSV laboratory-tested individual within Nebraska and any Nebraska death certificate between 2016 and 2021. The target population was Nebraskan residents.

Data Sources

Data sources derived from the State of Nebraska's Department of Health and Human Services (NE DHHS) Nebraska Electronic Disease Surveillance System (NEDSS) and the NE DHHS Vital Records Office for death certificate data. The RSV surveillance data was mostly electronic laboratory reporting (ELR), but also contained voluntary and syndromic respiratory laboratory reports. The RSV surveillance and death certificate data subset for the surveillance period (2016 – 2021). The American Community Survey (ACS) 1-year

midyear estimates were denominators for crude and specific annual case rates by age, sex, race, and ethnicity and crude mortality rate. ACS 5-year population estimates were directly adjusted (standardized) for RSV case rates by age (2016 – 2021), sex (2016 – 2021), race (2016 – 2019), and ethnicity (2016 – 2019). United States Census 2020 estimates were directly adjusted for RSV case rates by race (2020 – 2021) and ethnicity (2020 – 2021).

Key variables included in the RSV surveillance dataset include date of birth, sex, race, ethnicity, age, lab report date, lab report result, tested condition, local test codes, specimen source, LOINC, and local health department jurisdiction. In the death certificate dataset, variables included case first and last name, date of birth, sex, race, ethnicity, date of death, and RSV-specific ICD-10 and Supermicar codes.

Data cleaning and management

In cleaning the RSV surveillance dataset, the surveillance period was defined as January 1st, 2016 to December 31st, 2021. When the specimen sources contradicted the LOINC, lab reports were removed. Other contradicting conditions eliciting removal stemming from the LOINC included test type from ordered test and local test code. If no RSV status was reported or result was unrelated to a positive or negative status, then RSV lab reports were removed. When the LOINC was blank, other variables were assessed to determine if LOINC could be constructed for the RSV test type, ordering test, result comments, and local test code. All out-of-state lab reports to Nebraska were removed. Any non-RSV LOINC and antiquated LOINC were removed. Indications that noted an invalid test, e.g. duplicate test and did not complete test, were removed. Result comments unrelated to positive or negative RSV status or unable to determine if RSV lab report was RSV were removed.

The death certificate data were subset based on a given year, e.g. for 2016, January 1st – December 31st. De-duplication by unique death certificate ID was completed. Only death certificates reported to Nebraska were retained for analysis. RSV-specific ICD-10 codes were obtained from multiple sources, including the CDC's Supermicar website and the Center for Medicare and Medicaid Services ICD-10 support website (CDC, 2019) (*ICD-10 Resources | CMS*, n.d.).

RSV lab reports were de-duplicated by a NEDSS-unique patient ID and the most recent RSV lab reports regardless of status was selected into the de-duplicated dataset by year. RSV-specific mortality cases were determined using the RSV-specific ICD-10 codes and death certificate provider designations for any cause of death.

Created variables

Age was calculated from date of birth from the reported RSV laboratory report date. Stratification by week, month, and year was determined using the RSV lab report date. RSV test type was determined by a combination of values within the RSV surveillance dataset and LOINC codes and descriptions. RSV LOINC codes were reviewed primarily from the RSV surveillance dataset and matched to levels of RSV test type, including antigen-based tests, NAAT, and viral culture tests. To determine what RSV tests were able to detect multiple viruses or RSV only, the LOINC codes were reviewed along with RSV surveillance variables indicating a test that could detect multiple respiratory viruses.

The RSV laboratory test status could be reported as positive or negative. Using the result variable in the RSV surveillance dataset, character strings implied for a positive or negative test status were used to code the RSV test results. Example character strings for a positive RSV test included detected, "det", positive, "pos", and respiratory syncytial virus –

a known convention for select Nebraska laboratories. Character strings indicating a negative RSV test, included negative, "neg", not detected, or virus not detected. RSV-specified positive tests contained "RSV", "respiratory syncytial virus", or other abbreviated versions.

Regarding demographics, the RSV surveillance dataset contained date of birth, sex, race, and ethnicity. Age-specific values were categorized to reflect standard population categories. For ethnicity-specific rates reflective of standard populations, Hispanic or Latino, Non-Hispanic or Non-Latino, refused to answer, missing, or designated as unknown were natively or attributed values. For race-specific rates reflective of standard population categories: White, Black or African American, American Indian or Alaskan Native, Asian, Native Hawaiian or Other Pacific Islander, two or more races, some other race, missing, or unknown were natively or attributed values.

Linking RSV surveillance and death certificate datasets

Using SAS, the de-duplicated Nebraska RSV surveillance data was linked to the de-duplicated Nebraska death certificate data by year in a one-to-one exact match. Linkage between the RSV surveillance and death certificate datasets utilized shared, common variables, including date of birth, case last name, and case first name. A one-to-many linkage was also assessed in select years for comparative evaluation of the one-to-one linkage. Linkage was verified through complementary subsample frequency between linked and non-linked using SAS and Excel for cross-platform examination for all years. After data linkage was completed and verified, unique project-specific random identifiers were generated and personal identifying information unrelated to data analysis were stripped for privacy protection.

Trends and Rates

The annual case rate was defined as the number of de-duplicated RSV positive tests per year by the total number of de-duplicated RSV tests per year. The annual prevalence was the number of de-duplicated RSV positive tests per year by the midyear ACS 1-year estimated Nebraska population. The positivity rate was the total number of RSV positive tests by the total number of RSV tests per specified period.

The annual RSV mortality rate was the number of de-duplicated RSV-specific ICD-10 coded deaths by the midyear ACS 1-year estimated Nebraska population. The annual proportionate mortality ratio (PMR) for RSV was the number of de-duplicated RSV-specific ICD-10 coded deaths per specified time by the number of de-duplicated deaths per year.

Specific rates were calculated using de-duplicated laboratory surveillance data, death certificate, or linked datasets. Specific rates by age, sex, race, and ethnicity were calculated by year. The specific-rate numerator, Cr, was the number of RSV cases or RSV mortalities for a given level of the specific rate. The specific-rate denominator, Pi, was the midyear ACS 1-year estimated Nebraska population for a given level of that specific rate. All specific rates followed a general formula (Friis & Sellers, 2021):

$$Specific\ rate\ = \frac{Cr}{Pi}$$

Adjusted rates were calculated for age, sex, race, and ethnicity by year using the annual RSV specific case rates. Direct adjustment weight, Wi, was the standard weight applied for the i-th interval of the standard population, Psi was the population in the i-th interval for a given variable in the standard population, and $\sum Psi$ was the summation of the standard population. Direct adjustment was completed using a general formula (Friis & Sellers, 2021):

$$Direct\ adjustment\ weight\ (Wi) = \frac{Psi}{\sum Psi}$$

Direct adjustment was calculated using the ACS 5-year Nebraska standard population estimates for age-adjusted and sex-adjusted rates and the United States Census Standard Populations 2020 estimates in Nebraska for race-adjusted and ethnicity-adjusted. For any variable without a standardized population reported for a specific year, comparison between the previous year's standardized population was considered as a best approximation.

Cochran – Armitage test for trend

A Cochran – Armitage test for trend was completed for annual Nebraska RSV positivity rates with antigen-based tests decreasing and NAAT increasing comparatively over the surveillance period. The test for trend was two-sided test with the significance level set at 0.05. Specific p-values were reported for RSV by test type by RSV test only and RSV tests detecting multiple respiratory viruses. For inferential epidemiology, missing values for test variable were reported if necessary. Point (mean or median) imputation was completed for inferential procedures requiring non-missing values as needed.

Software

SAS 9.4 was utilized for data management, linkage, cleaning, variable frequency, and the Cochran – Armitage test for trends procedures and outputs. Microsoft Excel was the database source for the RSV surveillance, death certificate data, specific and direct rate calculations, tables, and figures. The Nebraska local health department map was created using Tableau.

Results

Data Cleaning and Management

The raw RSV surveillance dataset contained 193,815 observations. Removed 12,497 lab reports for being outside the surveillance period. The RSV surveillance datasets were cleaned for contradictory, out-of-jurisdiction, and non-RSV values along with the Nebraska death certificate datasets by year (Table 1). For complete details on data cleaning and management, please review Appendix A. There were 19,194 RSV lab reports removed. Between 2016 and 2021, RSV lab reports de-duplication process removed 33,991 observations.

Table 1: Summary of data management and linking RSV lab reports to death certificates by year.					
Year	RSV lab reports (n)	De-duplicated RSV lab reports	Death certificates (n)	De-duplicated death certificate (n)	Linked RSV lab reports to death certificates (n)
2016	8,894	6,886	17,179	17,179	1,111
2017	12,193	9,453	17,791	17,791	1,175
2018	15,397	12,652	18,063	18,063	2,107
2019	24,342	19,107	17,207	17,207	2,894
2020	24,067	20,425	19,703	19,703	1,406
2021	89,728	72,107	19,016	19,016	5,516
Total	174,621	140,630	108,959	108,959	14,209

Death certificates were extracted and subset by year using SAS. There were 4,344 out-of-state reported death certificates removed. No duplicate death certificates were found in any year. The resulting RSV surveillance dataset contained 170,401 lab reports with LOINC natively attached. The remaining lab reports were attributed LOINC from other RSV surveillance variables' values (n = 4,220), including result comments, ordered test descriptions and local test codes, for a total of 174,621 RSV lab reports for analysis. Tables 2 and 3 show the RSV detection status by test type. Appendix B shows a breakdown of RSV positive tests by the number of tests administered per year.

Table 2: RSV-specific lab tests by test results				
Test results	Antigen-based test	NAAT	Viral culture	Total
Negative	14,588	67,192	451	82,231
Positive	4,438	5,693	105	10,236
Total	19,026	72,885	556	92,467

Table 3: Multiple respiratory virus lab tests by test results				
Test results	Antigen-based test	NAAT	Viral culture	Total
Negative	42,090	33,356	2	75,448
Positive	3,357	3,416	0	6,773
Total	45,447	36,772	2	82,221

Of the 174,621 RSV lab reports, 54,018 (31%) were missing or unknown race and 151,101 (87%) were missing or unknown ethnicity. Of the 140,583 RSV de-duplicated with race and ethnicity as values, 44,173 (31%) and 121,698 (87%) were missing or unknown for race and ethnicity respectively. In contrast, Nebraska death certificate data missing or unknown race was 717 of 105,916 (0.6%) and 108 of 106,633 (0.1%). Please see Appendix B for supplemental tables and figures.

Trends and Rates

Crude measures for Nebraska RSV surveillance, death certificate data, and a linked one-to-one RSV surveillance and death certificate datasets are shown in Table 4 and Table 5.

Table 4: Crude measures Nebraska RSV lab reports, 2016 – 2021.			
Year	Annual prevalence (%)	RSV case rates per 1,000	RSV positivity (%)
2016	0.05	161.3	18.0
2017	0.06	124.3	13.9
2018	0.11	166.5	17.3
2019	0.15	151.4	15.3
2020	0.07	68.9	7.6
2021	0.29	76.5	7.4

| Table 5: Crude mortality measures in annual Nebraska RSV, 2016 – 2021.			
Year	RSV mortality rate per 100,000 linked	Proportionate mortality ratio (PMR) – linked (%)	RSV mortality rate per 100,000 – non-linked	Proportionate mortality ratio (PMR) – non-linked (%)
2016	0	0.00	0.73	0.09
2017	0.1	0.01	0.73	0.08
2018	0.4	0.04	1.45	0.16
2019	0.1	0.58	1.71	0.19
2020	0.0	0.00	1.45	0.14
2021	0.0	0.00	1.29	0.13

Crude RSV case rates per 1,000 and RSV positivity were less in 2020 and 2021 compared to previous surveillance period years. The highest annual RSV prevalence was in 2021 and the lowest in 2016. In contrast, the directly-adjusted rates for age, sex, race, and ethnicity were higher in 2020 and 2021 compared to previous surveillance period years and the annual RSV prevalence followed direct-adjusted rates. To determine spatial relationships between RSV laboratory testing in Nebraska, RSV positivity was reported through the surveillance period by local health department jurisdictions (Figure 1).

Figure 1: Nebraska RSV positivity by local health department, 2016 - 2021.
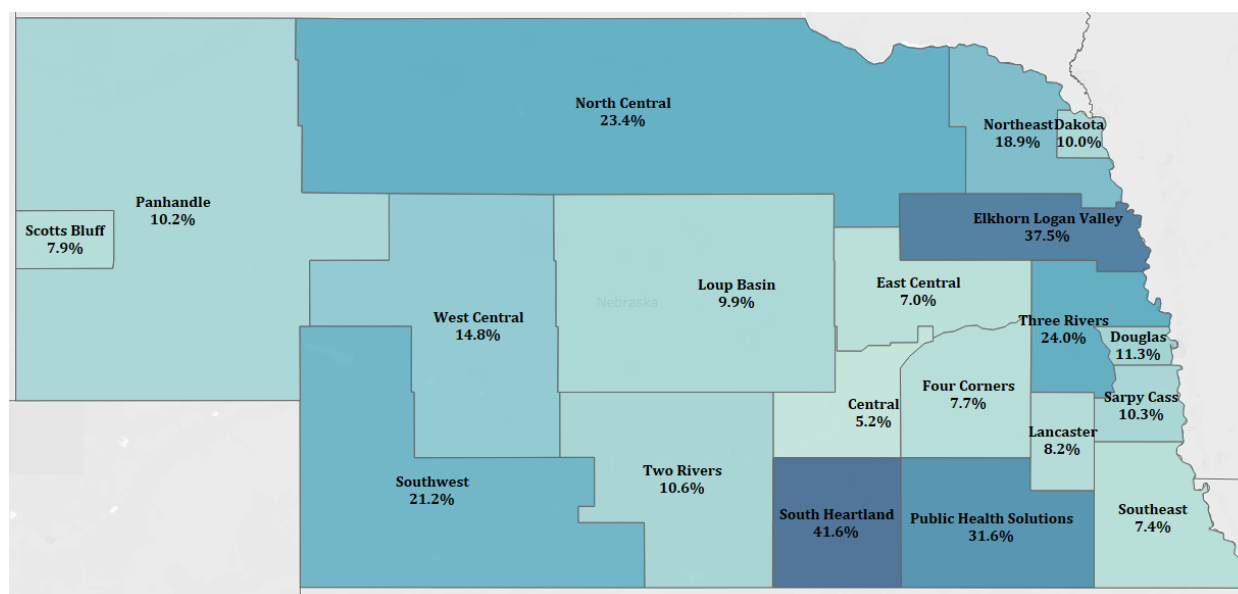
Large differences in the RSV positivity across the surveillance period were observed, e.g., 5.2% in the Central health department to 41.6% South Heartland health department. Dakota County health department had the lowest number of RSV testing across the surveillance period (n = 30) while Lancaster County health department had the highest (n = 12,614). RSV positivity rates in Nebraska shown in Figure 2, where laboratory tests ascertaining RSV only or RSV and other respiratory viruses were indicated. Only 2018 shows discrepancies between the laboratory testing for RSV or RSV and other respiratory viruses with the former about double the RSV positivity rate.

Figure 2: Nebraska annual RSV positivity trends, 2016 - 2021
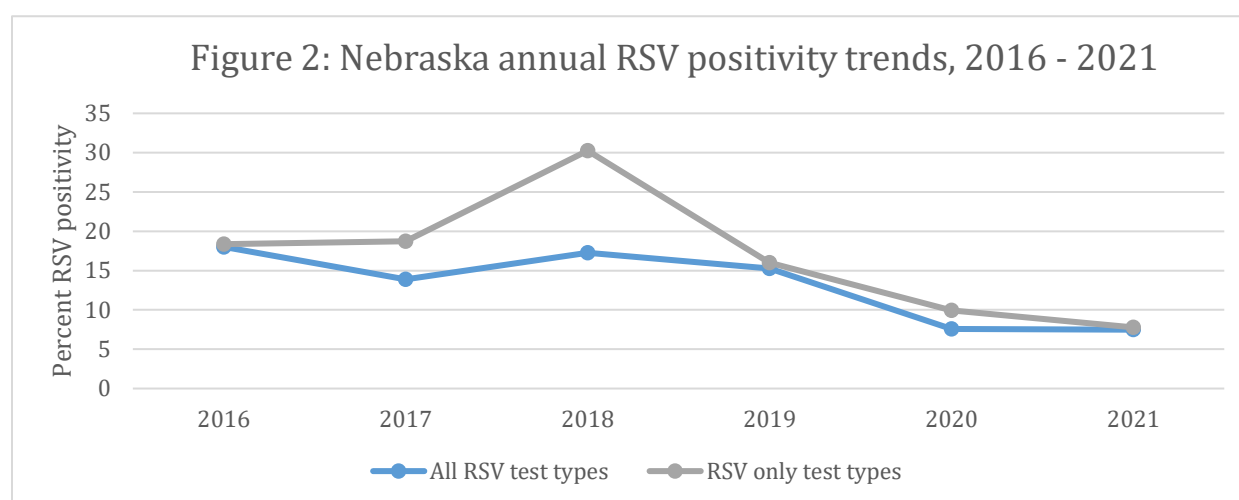
Crude mortality measures included Nebraska RSV mortality rates and PMR by the linked dataset and the death certificate dataset only respectively. The linked compared to non-linked demonstrated lower RSV mortality rates and lower PMR for all years. Since the linkage was the most recent RSV tests one-to-one linkage by year, a one-to-many linkage was completed (data not shown) for 2016 and 2017 to determine if there was greater RSV mortality when linked to more RSV tests per de-duplicated RSV case. However, this did not affect the RSV mortality case frequency for 2016 or 2017.

Age-adjusted RSV case rates were measured and modified per 100,000 as shown in Table 6.

Table 6: Nebraska age-adjusted RSV case rates per 100,000, 2016 – 2021						
Age-categories (years)	2016	2017	2018	2019	2020	2021
Under 5	52.4	215.2	320.0	430.2	292.2	922.2
5 – 9	0.4	11.7	60.3	55.1	49.9	214.1
10 - 14	0.5	6.7	34.3	26.9	31.5	200.2
15 – 19	0.1	6.0	21.7	22.1	36.7	196.3
20 – 24	0.1	5.1	8.0	15.9	34.1	161.3
25 – 34	0.2	10.4	16.4	34.8	72.7	313.5
35 – 44	0.6	12.6	18.8	38.5	75.1	287.5
45 – 54	0.6	16.7	29.6	52.0	85.2	279.7
55 – 59	0.6	14.0	22.3	42.7	56.2	175.1
60 – 64	0.5	13.5	24.4	45.9	59.4	189.0
65 – 74	1.1	22.5	44.0	90.5	115.9	339.4
75 – 84	0.8	15.8	34.6	80.1	84.8	268.2
85 +	0.4	8.9	24.3	57.2	62.4	183.5

The highest rates were seen in ages under 5 for all years. In Figure 3, age-adjusted RSV case rates in 2020 and 2021 exhibited increases compared to previous surveillance period years. In middle adult years (25 – 55), increases and fluctuation in trends were seen in 2020 and 2021 compared to 2018 and 2019. A tripling of under 5 RSV case rates from 2020 and 2021 is expected since the interseason 2021 RSV epidemic when social distance measures were relaxed in Nebraska.
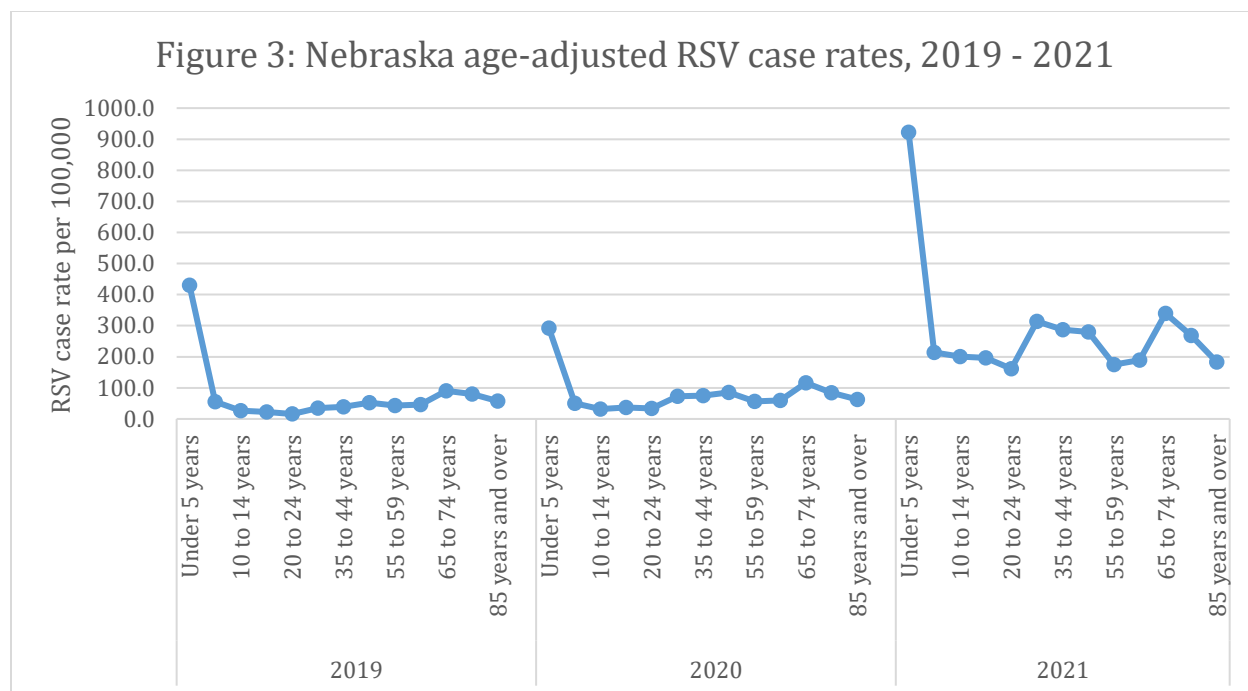
Figure 3: Nebraska age-adjusted RSV case rates, 2019 - 2021

Table 7 shows sex-adjusted RSV case rates through the surveillance period with no notable

differences in sex.

| Table 7: Nebraska sex-adjusted RSV case rates, 2016 - 2021						
Sex-Adjusted	**2016**	**2017**	**2018**	**2019**	**2020**	**2021**
Female	171.0	241.6	315.7	493.8	541.7	1959.6
Male	189.6	250.5	339.0	493.1	513.5	1764.6

Race-adjusted RSV case rates shown an increasing trend through the surveillance period

(Table 8).

Table 8: Nebraska race-adjusted RSV case rates per 100,000, 2016 – 2021.						
Race	2016	2017	2018	2019	2020	2021
White	100.4	141.0	209.8	537.2	594.6	2408.6
Black or African American	18.7	26.6	35.2	56.8	51.6	378.7
American Indian or Alaskan Native	1.5	1.9	3.2	6.9	13.2	35.2
Asian	1.7	1.7	2.8	6.2	9.6	31.7
Native Hawaiian or Other Pacific Islander	0.5	1.7	1.0	0.0	0.0	0.0
Two or more races	0.0	0.0	0.0	0.0	0.1	0.1
Some other race	12.1	12.1	8.2	0.0	0.0	0.0

In Figure 4, Black or African American, American Indian or Alaskan Native, and

Asian shown yearly increases in RSV rates with the highest increases in 2021.

Figure 4: Nebraska non-white race-adjusted RSV case rates, 2019 - 2021
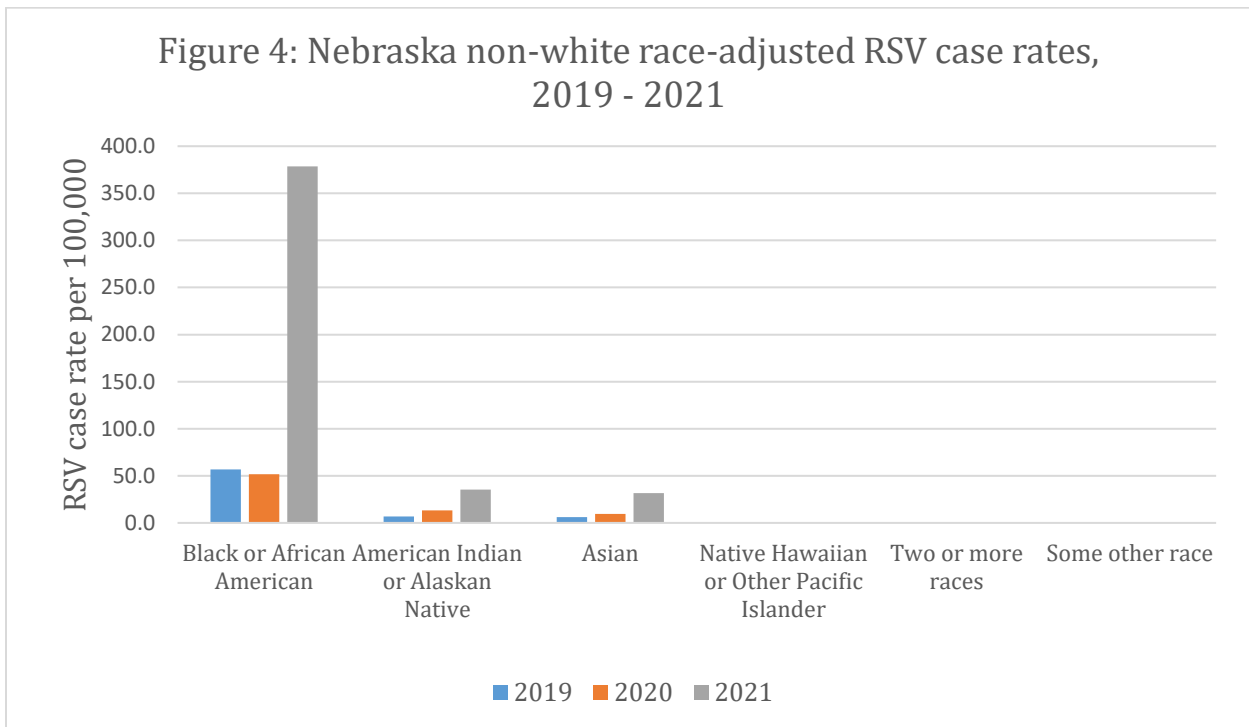
Some other race, two or more races, and Native Hawaiian or Other Pacific Islander had very low RSV cases. In analyzing Hispanic or Latino RSV case rates, increases from 2020 to 2021 with rates change from less than 1,000 per 100,000 to greater than 3,000 per 100,000 were observed (Table 9 and Figure 5).
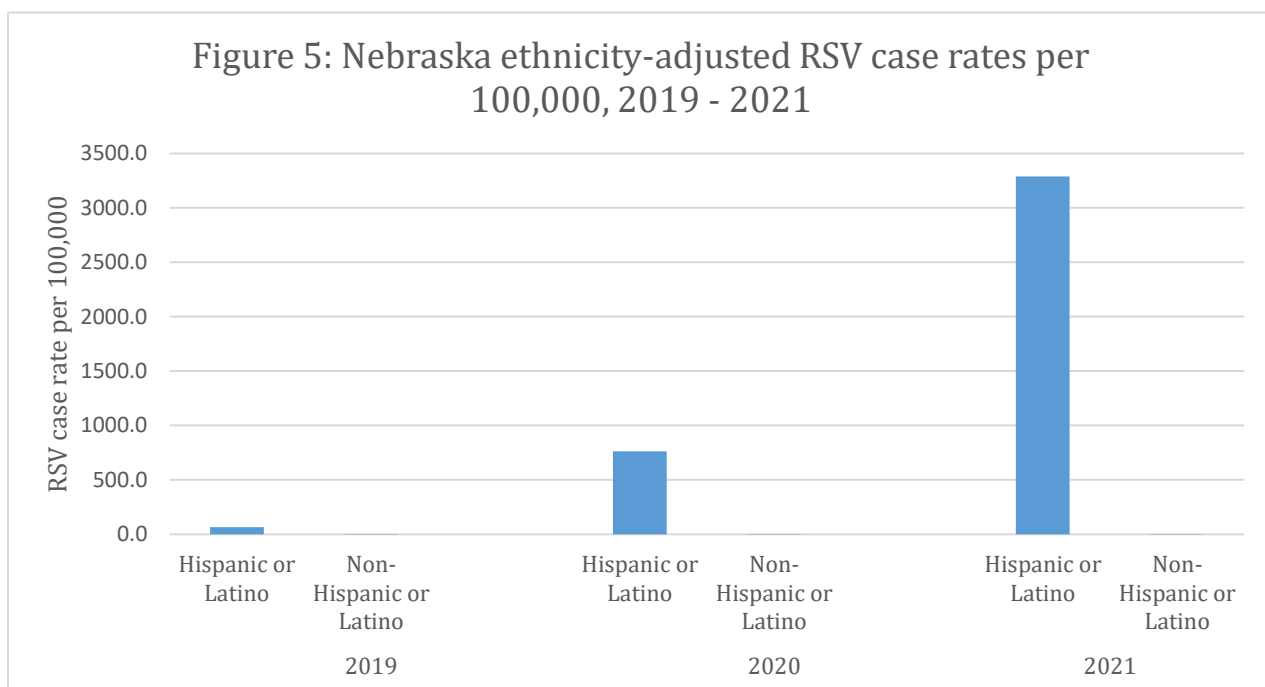

Figure 5: Nebraska ethnicity-adjusted RSV case rates per 100,000, 2019 - 2021

Table 9: Nebraska ethnicity-adjusted RSV case rates per 100,000, 2016 – 2021.						
Ethnicity	2016	2017	2018	2019	2020	2021
Hispanic or Latino	16.1	18.7	27.4	64.9	763.7	3290.4
Non-Hispanic or Latino	97.1	128.0	96.7	1.3	0.1	0.2

The RSV trends in Non-Hispanic or Non-Latino was very low, especially in years 2019 – 2021.

Cochran – Armitage test for trend

The Cochran – Armitage test for trend had no missing values requiring any point imputation. SAS executes the test for trend using the binomial proportions calculated in the

first row (antigen-based tests). The two-sided specific p-value was less than 0.0001

indicating a statistically significant linear trend, or there is evidence of linearly decreasing

antigen-based tests across the surveillance period compared to NAAT. (Table 10). The

frequency distribution (Figure 5) shown an increase for both RSV test types through the

surveillance period, but less so for antigen-based tests. When the Cochran – Armitage test

for trend was repeated for laboratory tests indicated for RSV only (Table 11), the two-sided

p-value remained significant and the overall pattern of antigen-based and NAAT RSV tests

increasing as time increases.

Table 10: Cochran-Armitage test for trend – RSV-specific test only							
Frequency	2016	2017	2018	2019	2020	2021	Total
Antigen-based	3792	6885	7592	10925	9901	25378	64473
NAAT	4822	5201	7761	13345	14137	64324	109590
Total	8614	12086	15353	24270	24038	89702	174063
Cochran-Armitage Trend Test							
Statistic (Z)							-74.6940
One-sided Pr < Z							<.0001
Two-sided Pr > |Z|						<.0001

Figure 5: Frequency distribution of RSV test types antigen-based or NAAT
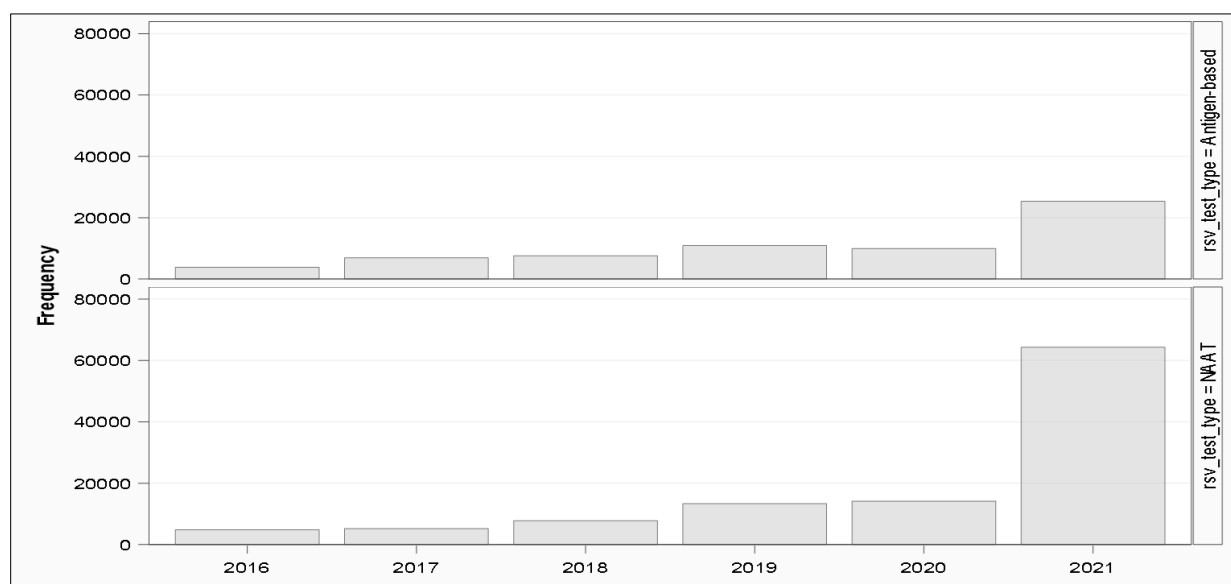
Table 11: Cochran-Armitage test for trend – RSV-specific test only							
RSV tests	2016	2017	2018	2019	2020	2021	Total
Antigen-based	3792	6885	7592	10925	9901	25378	64473
NAAT	3473	3272	2209	10258	11351	42255	72818
Total	7265	10157	9801	21183	21252	67633	137291
Cochran-Armitage Test for Trend							
Statistic (Z)							-74.2032
One-sided Pr < Z							<.0001
Two-sided Pr > |Z|							<.0001

Discussion

Multiyear surveillance reports can describe and analyze trends while identifying strengths and weaknesses in surveillance systems. Crude Nebraska RSV case rates and RSV positivity decreased in 2020 and 2021 compared to previous surveillance period years, which contrasts with the RSV annual prevalence, specific, and direct adjusted age, sex, race, and ethnicity rates. The latter denominator is an ACS 1-year midyear estimate while the former measures have denominators directly derived from the RSV surveillance dataset. As a result of these discrepancies in the crude rates, overall annual patterns and trends within a given measure may be more informative than between measures.

Nebraska RSV surveillance misses opportunities capturing race and ethnicity in contrast to Nebraska death certificate data, which is a common finding from these data sources. According to NAC regulations, race and ethnicity are not ELR-required as opposed to death certificates. Linking RSV surveillance and death certificate data exhibited very low RSV mortality rates, making specific and adjusted age, sex, race, and ethnicity mortality rates unfeasible. To ensure linking a RSV case to a corresponding death certificate, the linking incorporated first name, last name, date of birth, and subset by year. This one-to-one exact match linking may partially explain the very low RSV mortality rates in this

surveillance report. Given the one-to-many RSV testing and death certificate linkage for 2016 and 2017 demonstrating little change in RSV mortality cases, it is also possible that a correspondence issue between RSV testing status and death certificate reporting by provider or coders. In contrast to low Nebraska RSV linked observations, public health conditions with linkage between surveillance and death certificate data could improve through data completeness of race and ethnicity.

     A heightened emphasis on laboratory testing due to COVID-19 may uncover more RSV cases than would normally be anticipated, leading to increased rates in 2020 and 2021. The linked 2021 dataset was much larger than previous surveillance years and this is partially explained by the large number of lab reports in 2021. The 2020 and 2021 race and ethnicity-adjusted rates increased compared to 2019 rates in Black or African Americans, Asian, American Indian or Alaskan Native, Hispanic or Latino, which could be explained partially by increased access to free testing, increased concern regarding respiratory conditions due to the COVID-19 pandemic, and lack of RSV-specific positive status. Fourgeard (2021) reports that the interseason due to the COVID-19 pandemic in France involved lower, but more severe RSV positive results in adults, which contrasts with results observed in this report. Differences in surveillance and inpatient hospital in the interseason RSV epidemic in 2020 and 2021 may partially explain differences in results of cases based on setting. In the United States, O'Halloran (2021) reported racial and ethnic disparities (2009 – 2019) in age-specific and age-adjusted rates of influenza-like illnesses in the hospital setting. Blacks had the highest rate of influenza-like illness compared to other racial groups. In adults younger than 50, American Indian and Alaskan Natives were more

likely to be hospitalized than Whites. Thus, higher rates of RSV in Nebraska could lead to higher rates of hospitalization among racial minorities.

The Cochran – Armitage test for trend in Nebraska RSV testing trends was in partial contrast to national trends, which exhibited a reduction in antigen-based testing and increase in NAAT RSV test types (Midgely, et al, 2017). Nebraska exhibited increased antigen-based and NAAT RSV tests through the surveillance period, but the increase for antigen-based tests was less than NAAT. Misclassification bias in assessing RSV test types and RSV-specific positive status could bias away from the true value in either direction and affect the test for trend validity. Similarly, these are large sample sizes, which reduces random error when randomly sampled and increases the probability of a lower p-value. Since surveillance data does not represent a random sample of the target population, the increased sample size could be reducing the p-value arbitrarily.

Limitations in surveillance data include under reporting and incomplete data capture, e.g. laboratories misclassifying RSV test by LOINC. While attributing the RSV status for respiratory viral panel tests, the "positive" status may not be RSV-specified positive, but also positive for a different respiratory virus. This may overestimate RSV positive status within respiratory panel tests. The Nebraska RSV surveillance data captures only individuals seeking health care, which leads to a selection bias, e.g. only those seeking health care will receive an RSV test. With RSV infection, the clinical course is unaffected by identifying RSV as the infecting virus. This may reduce reporting and reduce correspondence between RSV positive status and RSV mortality further because providers may not recommend a viral laboratory test that doesn't affect clinical care. In race and ethnicity, the high percentage of missing or unknown values may affect the precision of the

specific and adjusted rates. These limitations affect generalizability to all Nebraskan RSV

infections; in particular, subclinical or those lacking regular health care access.

Alternatively, the increase in race and ethnicity adjusted RSV case rates in 2020 and

2021 could be an indication of access to care. Given free laboratory testing and increased

concern of COVID-19 infection, more underinsured or those lacking insurance may be more

inclined to be tested fearing COVID-19 consequences, but are incidentally infected with

RSV and not SARS-CoV-2. The increase in middle-aged adult RSV case rates may also be an

artifact of free, concerned, and available testing due to the COVID-19 pandemic. Since RSV

can reinfect humans continuously through the lifespan, the increased middle aged RSV case

rates in 2021 may be an indication of relaxed social distancing measures and RSV epidemic

changes in seasonality and severity from the 2020 lockdowns in Nebraska (Baker et al.,

2020).

Further research to improve data quality in Nebraska RSV surveillance cases

regarding specificity of positive status for a specific virus in respiratory panel tests, race,

and ethnicity is warranted. This may involve improved automation of data capturing and

portability mechanisms by local health department investigators and public health

laboratories. Nebraska local health departments show differences in RSV positivity across

the surveillance period. In small, rural local health departments, testing may be limited by

cost, provider availability, health insurance status, and distance travelled to a provider

compared to large, urban local health departments, which could overestimate RSV

positivity compared to rural challenges in RSV testing. Surveying health care providers in

these jurisdictions regarding RSV testing and positivity may provide insight into these

challenges. Surveys of health care seeking behavior during the COVID-19 pandemic may

elicit improved understanding, especially if RSV case rates truly increased due to free testing and increased access or if an actual RSV case rates increased.

Multiyear RSV surveillance reports are infrequently completed and reported at the state-level with specific and direct case rates by demographics. Challenges in RSV laboratory surveillance reduce precision and quality of RSV case rates; however, reporting these challenges highlights considerations to improve RSV public health surveillance and the guiding regulations. Nebraska multiyear RSV laboratory surveillance and death certificates indicates discrepancy between provider-noted death certificates and laboratory surveillance testing and results. Higher RSV case rates during in 2020 and 2021 – coincident with the COVID-19 pandemic – are imprecise given current challenges with laboratory reporting in Nebraska.

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Appendix A – Data Cleaning Details

Reasons for removal of some RSV surveillance observations from the analysis included

contradiction of RSV specimen source tests (n=39), multiplex PCR RSV positive report

without specifying the virus (n=1), RSV lab report lacking details on LOINC (n=5), specimen

type (n=40), test type (n=5), and out-of-state lab reports (n=17,455), non-RSV LOINC-

specific lab reports (n=5), antiquated RSV LOINC-specific lab reports (n = 10),

contradictory RSV lab reports regarding LOINC-indicated test type and laboratory-

indicated test type (n = 185), RSV lab reports indicated as invalid tests (n = 83), e.g.

duplicate test not completed or expired test, RSV lab reports because test result is a

nonsense comment and no other test result indication could be determined (n = 1,126) ,

e.g. "NOTP CLIENT SENT WRONG SPEC PLS CANCEL CONTACT KIM AT CLIENT 1415 4.9.19

DT," and RSV lab reports because the test results were blank and no other test result

indication could be determined (n = 239).

Appendix B – Supplemental Tables and Figures

Table A: RSV positive status by RSV test type and year					
Year	Antigen-based tests, positive	NAAT, positive	Viral culture, positive	Total positive tests	Total tests administered (% positive)
2016	643	448	32	1,123	8,894 (12.6)
2017	693	556	23	1,272	12,193 (10.4)
2018	840	1,424	10	2,274	15,397 (14.8)
2019	1,741	1,439	23	3,203	24,342 (13.2)
2020	645	772	10	1,427	24,065 (5.9)
2021	2,582	3,924	7	6,513	89,728 (7.3)
Total	7,144	8,563	105	15,812	174,619 (9.1)

Figure A: Race-adjusted Nebraska RSV case rates, 2019 - 2021
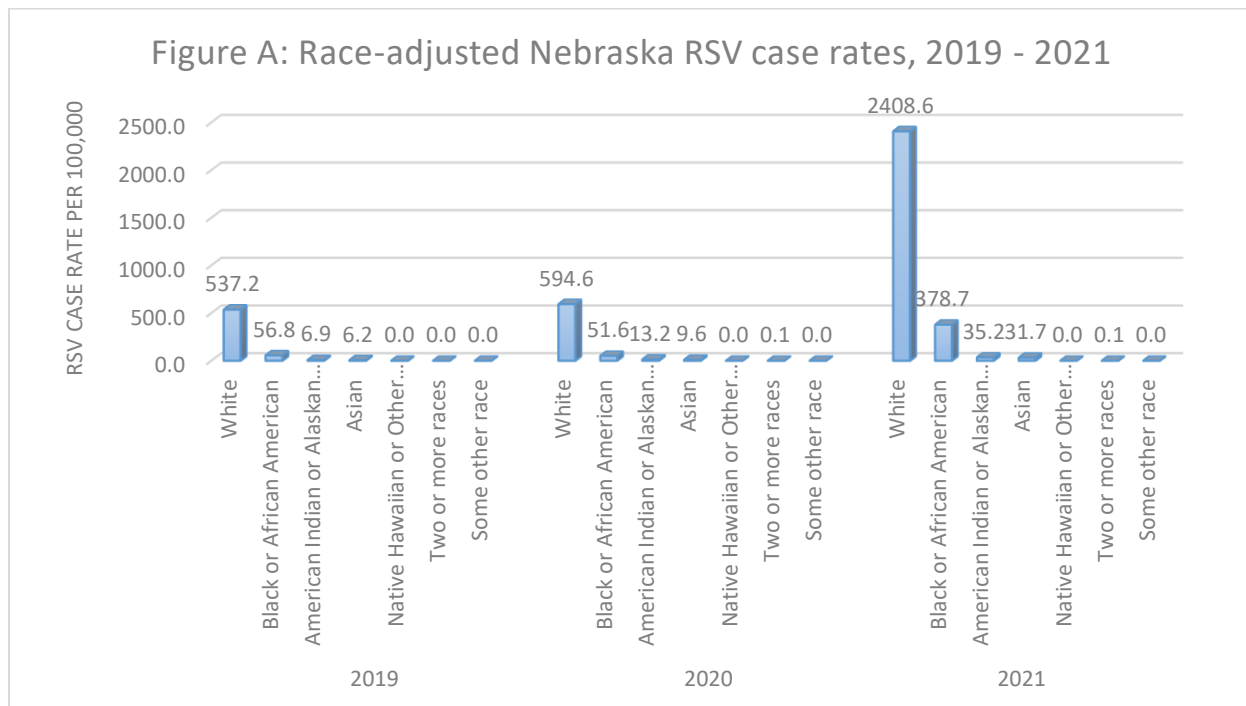
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Professional Development

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