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Increase in Detection of Respiratory Syncytial Virus Among Older Adults in Arizona: An Association With Changes in Testing Practices

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Abstract

Objectives: Respiratory syncytial virus (RSV) is a common cause of respiratory illness, health care visits, and hospitalizations. Arizona, which began conducting laboratory surveillance in 2004, has noted an increase in RSV cases (defined as a laboratory-positive result) among adults aged ≥65, concurrent with increasing reports from polymerase chain reaction (PCR) testing. We assessed whether the shift in the age distribution of reported RSV cases resulted from a change in RSV testing practices.

Methods: We used data on laboratory-confirmed RSV cases reported during 2013-2017 from the statewide surveillance system to assess the frequency of test types (rapid antigen, immunofluorescence assay, PCR, and viral culture) by age groups across RSV seasons, and we used logistic regression to estimate changes in odds of receiving a PCR test. We used statewide emergency department hospital discharge data for the same period to assess testing practices regardless of test result.

Results: The overall proportion of PCR tests among RSV cases increased significantly, from 22% in 2013 to 55% in 2017 ($P < .001$). The percentage of RSV cases among adults aged ≥65 also increased significantly, from 4% in 2013 to 11% in 2017 ($P < .001$) of RSV cases. Adults aged ≥65 had more than 8 times the odds of positive PCR results than children aged <5, both in crude (odds ratio [OR] = 8.8; 95% CI, 7.6-10.2) and season-adjusted (adjusted OR = 8.1; 95% CI, 7.0-9.5) models. Hospital discharge data corroborated increased RSV PCR usage from 2013 to 2017.

Conclusion: Increasing RSV rates among adults aged ≥65 are likely a result of changes in testing practices. This age group may need more targeted intervention and future vaccination.

Keywords

RSV, PCR, older adults

Respiratory syncytial virus (RSV) is a common cause of respiratory illness, physician office visits, hospitalizations, and even death.[1] RSV is the most frequently identified cause of lower respiratory tract illness in infants and young children.[2,3] Attention to RSV infections in older adults has increased in recent years, in part because of outbreaks in long-term care facilities.[2] Although the full burden of disease in this age group is unknown, 1 study found that 12% of acute respiratory illness in medically attended adults aged ≥50 was caused by RSV.[4] Another study found that each year, 2%-10% of older community-dwelling adults and 5%-10% of older adults living in congregate settings were infected with RSV.[5] Outside supportive care, no treatment or RSV vaccine exists; however, an estimated ≥50 RSV vaccines and therapeutic agents are in phase 2 and phase 3 clinical trials.[6] Describing the true epidemiology of RSV before vaccine introduction is a public health priority.[7] Understanding the incidence of RSV across age groups can ensure that vaccines and other resources are appropriately targeted and allocated and will provide baseline data for assessing the effect of RSV vaccine introduction.

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As of 2018, only a dozen states required RSV to be reported to the health department upon diagnosis or laboratory confirmation.[8] Since 2004, laboratories in Arizona have been required to report positive RSV results to the public health department for surveillance purposes and must submit case information, including data on demographic characteristics and test results, within 5 working days. During the 2009-2010 through 2012-2013 RSV seasons, >90% of reported cases with a known age were among children aged <5 each season; that proportion has decreased in recent years, whereas the proportion of cases among adults aged ≥65 has increased.[9]

Laboratory methods to test for RSV include rapid antigen tests (eg, single-antigen detection test), immunofluorescence assay tests, polymerase chain reaction (PCR) tests, and viral culture. The most frequent test performed for RSV is a rapid single-antigen detection test, because of its low cost, ease of use, and prompt receipt of results.[10] Barriers to using other tests, such as personnel laboratory training or longer time to receive results, limit their usefulness.[11] In 2008, the US Food and Drug Administration approved multiplex PCR tests for respiratory pathogens, including RSV, for diagnostic use.[12] The multiplex PCR respiratory panel allows health care providers to test a patient for multiple pathogens at once with high sensitivity and rapid detection. Before the availability of the multiplex PCR respiratory panel, health care providers might have requested a test for only a suspected pathogen, requested culture (with subsequent longer detection times), or managed patients empirically without diagnostic testing. PCR has been an increasingly common diagnostic test for RSV in the United States in the past decade, and PCR reports to the Centers for Disease Control and Prevention's National Respiratory and Enteric Virus Surveillance System for RSV increased 200-fold, with a simultaneous decline in antigen-based reports.[10,13]

We assessed whether the shift in the age distribution of reported RSV cases in Arizona over time resulted from a change in RSV testing practices, perhaps capturing a greater proportion of cases in later years than in earlier years among adults aged ≥65 who might not have been tested for RSV otherwise. We explored trends in age and test type initially and found a corresponding relationship between age and testing,[14] but we further examined available data to make a stronger case. We also examined 4 years of surveillance data to identify whether the observed age shift might be associated with changes in the types of laboratory tests used to confirm RSV during this period.

Methods

Reported Laboratory Data

We used Arizona's statewide electronic surveillance system, Medical Electronic Disease Surveillance Intelligence System,[15] to identify RSV cases. Laboratories report positive RSV results routinely to the Arizona Department of Health Services, using the same reporting mechanisms as for other communicable diseases.[16] Reports contain patient identifiers, demographic information (eg, age, sex, home address), and testing information (eg, type of test performed).

We defined a case as a laboratory-positive result. We defined RSV seasons as October 1 through September 30 of the following year. We included seasons 2013-2014 through 2016-2017 in our analysis. We defined age groups as 0-4, 5-14, 15-64, and ≥65.

We categorized reported tests as rapid antigen tests, PCR tests, direct fluorescent antibody/indirect fluorescent antibody (DFA/IFA) tests, and viral culture. A total of 19 856 laboratory cases were reported across all 4 seasons. We removed duplicate test types when a case had multiple reports of the same test type in a season (n = 1064). Because multiple positive test results might have been reported for a single person, we conducted the analysis at both the laboratory result level (all tests included) and person level (using only 1 test type per case). When multiple tests types were reported for a single case (n = 534), we used the following descending hierarchy of tests to select the test type to use in our person-level analysis: PCR, viral culture, DFA/IFA, and rapid antigen. For example, if a case had a PCR test and a rapid antigen test, we retained the PCR test for analysis. We excluded cases in which the person's age was unknown (n = 51) or the test type was uncategorizable (n = 975), leaving 17 232 cases in the analysis. We calculated the frequency of test type among RSV-positive laboratory reports and the distribution of cases among age groups. We used the Pearson χ^2 test to assess differences in test type by age group across seasons. We used multivariate logistic regression to assess the association of age group or RSV season with the odds of a case with a positive PCR result. We assessed interactions between age group and season by using a type 3 joint test. We considered $P < .05$ to be significant.

Hospital Discharge Data

To explore changes in RSV testing practices for the same period, we used hospital discharge data (HDD)[17] to identify visits in which an RSV test was performed. HDD include information on diagnoses and dates of visit and discharge, as well as data on patient demographic characteristics for all hospital visits at nonfederal hospitals in Arizona. HDD also include Current Procedural Terminology (CPT) codes,[18] which are used by health insurers to determine the reimbursement amount for a procedure. We identified visits with RSV PCR CPT codes 87633 and 87632 (respiratory virus panel testing for multiple pathogens, including RSV), 87798 (tests for RSV only), 87631 (tests for influenza and RSV), and RSV rapid antigen CPT codes (87807 and 87420). HDD include only CPT codes for emergency department (ED) visits if the person was not admitted; as such, we excluded admitted patients from analysis. Because HDD were used to examine testing practices, we did not consider test results or discharge diagnoses.

Table 1. Distribution of respiratory syncytial virus (RSV) test types, by age group, during the 2013-2014 to 2016-2017 RSV seasons, Arizona[a]

Age group, y	2013-2014 RSV season test type, no. (%)					2014-2015 RSV season test type, no. (%)					2015-2016 RSV season test type, no. (%)					2016-2017 RSV season test type, no. (%)				
	PCR	Culture	DFA/IFA	Rapid	Total	PCR	Culture	DFA/IFA	Rapid	Total	PCR	Culture	DFA/IFA	Rapid	Total	PCR	Culture	DFA/IFA	Rapid	Total
0-4	446 (19)	53 (2)	508 (21)	1403 (58)	2410 (90)	1640 (39)	61 (1)	510 (12)	1953 (47)	4164 (84)	1469 (42)	44 (1)	153 (4)	1794 (52)	3460 (81)	1880 (46)	73 (2)	319 (8)	1826 (45)	4098 (77)
5-14	36 (45)	4 (5)	18 (23)	22 (28)	80 (3)	157 (66)	6 (3)	20 (8)	55 (23)	238 (5)	112 (84)	0	3 (2)	19 (14)	134 (3)	166 (76)	14 (6)	2 (1)	35 (16)	217 (4)
15-64	47 (47)	8 (8)	16 (16)	30 (30)	101 (4)	217 (79)	9 (3)	16 (6)	31 (11)	273 (5)	234 (84)	3 (1)	3 (1)	37 (13)	277 (6)	332 (84)	3 (1)	7 (2)	53 (13)	395 (7)
≥65	58 (59)	3 (3)	25 (26)	12 (12)	98 (4)	231 (78)	13 (4)	30 (10)	21 (7)	295 (6)	364 (89)	5 (1)	9 (2)	30 (7)	408 (10)	519 (89)	1 (<1)	7 (1)	57 (10)	584 (11)
Total	587 (22)	68 (3)	567 (21)	1467 (55)	2689 (100)	2245 (45)	89 (2)	576 (12)	2060 (41)	4970 (100)	2179 (51)	52 (1)	168 (4)	1880 (44)	4279 (100)	2897 (55)	91 (2)	335 (6)	1971 (37)	5294 (100)

Abbreviations: DFA/IFA, direct fluorescent antibody/indirect fluorescent antibody; PCR, polymerase chain reaction.
[a]Data source: Arizona Department of Health Services.[15]

We defined RSV seasons in HDD consistent with definitions used for RSV laboratory-confirmed cases, and we calculated the frequency of RSV test type, the distribution of age groups among people tested for RSV, and the stratified frequency of test type by age group across seasons. We calculated frequencies at the test level and counted per person per visit. We calculated rates per 100 000 ED visits to account for variation in age-specific ED visits each season. We performed all analyses using SAS version 9.4 (SAS Institute Inc). The Centers for Disease Control and Prevention Human Subjects Review Board determined this study to be nonresearch.

Results

Reported Laboratory Data

A total of 17 232 RSV cases were reported during the study period, with 2689-5294 RSV cases reported each season (Table 1). Approximately 10% of cases had >1 type of test reported. The age distribution differed significantly across RSV seasons ($P < .001$). The proportion of reported cases that occurred among infants and children aged <5 declined from 90% (2410 of 2689) during the 2013-2014 RSV season to 78% (4098 of 5294) during the 2016-2017 RSV season. Conversely, the proportion of cases among adults aged ≥65 increased from 4% (98 of 2689) to 11% (584 of 5294) during the same RSV seasons. The RSV incidence rate increased from the 2013-2014 RSV season to the 2016-2017 RSV season among all age groups. The RSV incidence rate per 100 000 population increased from 7 to 50 cases among people aged ≥65 and from 557 to 933 cases among infants and children aged <5.

During the same period, the proportion of positive PCR test results increased significantly, from 22% (587 of 2689) of cases with available test information during the 2013-2014 RSV season to 55% (2897 of 5294) during the 2016-2017 RSV season ($P < .001$; Table 1). More than half (57%) of PCR tests during the 2016-2017 RSV season were identified as respiratory panels; insufficient information was available for the remaining tests to determine single-organism or multiorganism detection capabilities.

Both later season and older age group (vs earlier seasons and younger age groups) were significantly associated with higher odds of a PCR report (Table 2). Cases reported during the 2016-2017 RSV season had approximately 4 times the odds of including a positive PCR test than cases reported during the 2013-2014 season in both crude (odds ratio [OR] = 4.3; 95% CI, 3.9-4.8) and age-adjusted (adjusted OR [aOR] = 3.9; 95% CI, 3.5-4.4) models. Adults aged ≥65 had more than 8 times the odds of being tested by PCR compared with children aged <5, both in crude (OR = 8.8; 95% CI, 7.6-10.2) and season-adjusted (aOR = 8.1; 95% CI, 7.0-9.5) models. We found a significant interaction between age group and season ($P = .001$), suggesting possible evidence of an interaction between the effects of age and season in the relationship of being tested by PCR.

HDD. More than 2 million ED visits were recorded each season. We found increasing numbers of RSV PCR tests ordered each season in HDD, whereas the number of RSV rapid antigen tests was similar across seasons (Table 3).

Among adults aged ≥65, the number of RSV PCR tests ordered per 100 000 ED visits increased from 11 during 2013-2014 to 43 during 2016-2017 ($P < .001$); we observed an annual increase for all age groups (Table 4). Use of the influenza and RSV panel and multiplex respiratory panel increased more than the RSV-only PCR test. Although the influenza and RSV panel was the most commonly used PCR test for adults aged ≥65, the multiplex respiratory panel had the largest percentage increase over time.

Discussion

Across 4 RSV seasons in Arizona, the rate of laboratory-reported RSV cases per 100 000 population among adults aged

Table 2. Crude, adjusted, and stratum-specific odds ratios (ORs) for receiving a PCR test, by respiratory syncytial virus (RSV) season and age group, 2013-2017, Arizona[a]

Variable	Crude OR (95% CI)	Adjusted OR (95% CI)
RSV season		
2013-2014	1.00 [Reference]	1.00 [Reference]
2014-2015	2.9 (2.7-3.3)	2.9 (2.6-3.3)
2015-2016	3.7 (3.3-4.2)	3.5 (3.1-3.9)
2016-2017	4.3 (3.9-4.8)	3.9 (3.5-4.4)
Age group, y		
0-4	1.00 [Reference]	1.00 [Reference]
5-14	3.8 (3.2-4.5)	3.8 (3.2-4.6)
15-64	6.2 (5.3-7.2)	5.9 (5.1-6.9)
≥65	8.8 (7.6-10.2)	8.1 (7.0-9.5)
Stratum-specific with interaction[b]		
2013-2014 and age ≥65	1.00 [Reference]	1.00 [Reference]
2014-2015 and age ≥65	—[c]	15.9 (11.8-21.4)
2015-2016 and age ≥65	—[c]	36.4 (26.2-50.6)
2016-2017 and age ≥65	—[c]	35.2 (26.6-46.4)

Abbreviation: PCR, polymerase chain reaction.
[a]Data source: Arizona Department of Health Services.[15]
[b]$P = .001$. A type 3 joint test was used to determine significance, with $P < .05$ considered significant.
[c]Stratum-specific terms with interaction can be assessed only in the adjusted model. Includes 1 test per case.

≥65 increased from 7 to 50, a much greater increase than identified in other age groups. The proportion of cases reported by PCR tests among all age groups increased during the same period, from 22% to 55%, and especially among adults aged ≥65 (from 59% to 89%), and an increase in PCR use has been observed nationally.[10,13] We found that the relationship between PCR usage and age was true across seasons, such that as PCR use increased, the rate and proportion of cases among adults aged ≥65 increased. Although PCR reports were more likely during later seasons than during earlier seasons, age ≥65 was independently associated with PCR testing and the interaction between season and age group was significant.

Although our surveillance data included only positive test results, the use of HDD allowed us to examine changes in testing practices. We observed an increase in the use of PCR testing in EDs during this same period among all age groups, especially use of the multiplex respiratory panel, and changes were more prominent among adults aged ≥65. This finding supports our hypothesis that multiplex respiratory panels are being used more frequently than other test types in this age group, regardless of result.

Our observations of an increasing incidence of RSV infections among adults aged ≥65, and our findings of increasing PCR use,[10,13] are consistent with the literature.[4,5,19] The changes in testing practices during the same period suggest that this epidemiologic shift in the ages of reported cases might be the result of increased use of PCR-based respiratory viral panels and improved detection of RSV among older adults who might not have been tested for RSV otherwise. Using PCR, particularly as a respiratory panel or in combination with influenza testing, is becoming increasingly popular because of the advantages and efficiencies of a timely diagnosis. Use of multiplex respiratory

Table 3. Respiratory syncytial virus (RSV) rapid antigen test compared with any RSV PCR test, rate per 100 000 ED visits, 2013-2017, Arizona[a]

	No. (rate)		
RSV season	RSV rapid antigen test	Any RSV PCR test	Total ED visits, no.
2013-2014	6745 (326)	1807 (87)	2 071 281
2014-2015	8871 (387)	3137 (137)	2 291 911
2015-2016	7447 (313)	4747 (199)	2 382 426
2016-2017	7168 (312)	5087 (221)	2 300 931

Abbreviations: ED, emergency department; PCR, polymerase chain reaction.
[a]Data source: Arizona Department of Health Services.[17]

Table 4. Respiratory syncytial virus (RSV) PCR test type use counts[a] and rate per 100 000 hospital emergency department visits per RSV season, by age group, 2013-2017, Arizona[b]

Age group, y	RSV only PCR (n = 8087)					Respiratory panel PCR (n = 8189)					Influenza and RSV PCR (n = 5050)				
	No. (rate)					No. (rate)					No. (rate)				
	2013-2014	2014-2015	2015-2016	2016-2017	Total, no.	2013-2014	2014-2015	2015-2016	2016-2017	Total, no.	2013-2014	2014-2015	2015-2016	2016-2017	Total, no.
0-4	828 (387)	1373 (607)	1788 (780)	1904 (887)	5893	681 (318)	1283 (567)	1999 (872)	2306 (1075)	6269	230 (107)	501 (222)	564 (246)	459 (214)	1754
5-14	144 (76)	291 (140)	420 (199)	390 (196)	1245	91 (48)	263 (126)	454 (215)	431 (217)	1239	59 (31)	132 (63)	197 (93)	148 (75)	536
15-64	212 (16)	190 (13)	217 (14)	228 (15)	847	28 (2)	135 (9)	209 (14)	222 (15)	594	154 (11)	279 (19)	900 (58)	1112 (75)	2445
≥65	20 (6)	25 (7)	27 (7)	30 (7)	102	1 (0)	21 (6)	28 (7)	37 (9)	87	13 (4)	68 (19)	106 (27)	128 (32)	315

[a]Cases can be counted in >1 category.
[b]Data source: Arizona Department of Health Services.[17]

panels has been encouraged and recommended in recent literature.[20,21]

Although PCR use also increased among children aged <5 during the 4 RSV seasons, rapid antigen RSV tests were most common in this age group. The higher proportion of rapid antigen RSV tests in the youngest age category might reflect that health care providers are more likely to suspect RSV in infants and young children than in adults aged ≥65 and is likely the result of an established practice behavior that will presumably continue. Although recent literature has recognized RSV in older populations,[22] health care providers might not consider RSV as readily among adults aged ≥65 as in children,[1] and the lower sensitivity of RSV antigen testing among older age groups[23] compared with younger age groups might further discourage health care providers from ordering antigen tests for older adults.

Although sensitivity and specificity vary depending on viral target, age of patient, specimen type, and duration of symptoms before testing, PCR tests are both more sensitive and more specific than rapid antigen tests for detecting RSV. Rapid antigen tests have approximately 80% sensitivity and 97% specificity,[24] whereas multiplex respiratory panels (Biofire Respiratory Panel, Biomerieux) have approximately 95% sensitivity and 99% specificity. The increase in reported RSV cases might be a result of improved detection because of the use of a more sensitive test, such as PCR, instead of rapid tests.[25] On the other hand, PCR tests are also more specific than rapid tests, which would lead to fewer false-positive tests reported. Nevertheless, changes in sensitivity and specificity cannot explain the large increase of reported RSV cases among people aged ≥65 that we observed.

Limitations

This study had several limitations. First, only positive RSV test results are reportable to the Arizona Department of Health Services. As such, changes in the type of testing ordered could not be confirmed using surveillance data; the findings from these data cannot rule out differences in test performance in different ages versus differences in testing practices. Only ED visits without hospital admission could be used from HDD, and these visits might not reflect testing practices in inpatient or outpatient clinical settings. Second, test type coding errors may have occurred in HDD. Third, for the influenza and RSV panel and the multiplex respiratory panel, RSV might not have been the suspected infectious agent or the diagnosis. Arizona had a high-incidence influenza season in 2015-2016, which could have led to more panel testing than usual, resulting in increased RSV case finding. Fourth, test type is not specified in surveillance data for all reports, and the proportion of observations with missing test type varied across seasons. Laboratories reporting via electronic laboratory reporting are more likely to perform PCR tests that can be more easily categorized via LOINC (Logical Observation Identifiers Names and Codes) and SNOMED (Systematized Nomenclature of Medicine) codes, whereas rapid antigen tests often come in through fax and might not clearly specify test type. Classification of test types improved through the seasons as more laboratories begin using electronic laboratory reporting to report positive cases to the Arizona Department of Health Services. Thus, a PCR test might be more likely to get properly categorized than a rapid antigen test. Assuming that all uncategorized tests were rapid antigen tests would only strengthen our findings in that PCR tests would comprise an even smaller proportion in 2013-2014 and 2014-2015.

Conclusion

Because Arizona is one of a dozen states in which RSV is a reportable condition, we are in a unique position to characterize trends at a state level. A strength of our data is that we are not limited to specific populations, such as hospitalized people or long-term care residents. Whereas previous studies have described the clinical importance and burden of RSV infections among older adults, our analysis might help address the gap in RSV epidemiology at a broader population level and provide background for interpreting any

observed demographic shifts. RSV might cause a greater incidence of disease in older populations than previously recognized, although this is likely not a new phenomenon but a result of testing practice changes. More targeted intervention and future vaccination might be necessary in this age group, particularly as the aging population continues to grow.

Authors' Note

A subset of this analysis was published in a brief Notes From the Field in *Morbidity and Mortality Weekly Report* (https://www.cdc.gov/mmwr/volumes/68/wr/mm6808a4.htm). This article has not been submitted or published elsewhere.

Declaration of Conflicting Interests

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