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National and regional modeling of distinct RSV seasonality thresholds for antigen and PCR testing in the United States

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ABSTRACT

Background: PCR tests now outnumber antigen tests for the diagnosis of respiratory syncytial virus (RSV) infection in the US. Recent analyses have shown that the traditional 10% positivity threshold to define an RSV season by rapid antigen testing was inappropriate for real-time PCR testing, for which 3% positivity appeared more appropriate.

Objective: To respectively model antigen (10%) and PCR (3%) positivity thresholds at national and regional levels using a large dataset of RSV testing results from US hospital-affiliated laboratories.

Study design: From 2011–2016, 599 laboratories participated in a national RSV surveillance program (RSVAlert®). For laboratories with ≥10 tests for ≥30 weeks of a season, national and regional test numbers and positivity were summarized by test type overall, by season, and weekly within each season. Test type positivity thresholds were used to calculate season onset and offset.

Results: A seasonal average of 543,387 RSV tests was reported. PCR testing increased from 26% in 2011–2012 to 72% in 2015–2016. Overall, national positivity was 15.6% for antigen and 8.3% for PCR testing. National RSV season onsets and offsets were comparable using the 10% antigen and 3% PCR thresholds, but PCR-defined seasons generally started and ended later than antigen-defined seasons. Regionally, there were fewer outlier estimates of RSV season length when the predominant regional test type was used to define the season.

Conclusion: RSV positivity rates differed by test type, likely due to differential clinical use of the tests. These findings support the use of distinct positivity thresholds by test type.

1. Background

Respiratory syncytial virus (RSV) is the most common cause of lower respiratory tract illness in infants and young children [1], and is estimated to cause up to 75% of all infant bronchiolitis and 37% of all pediatric community-acquired pneumonias [2,3]. Preterm infants ≤35 weeks gestational age and children with certain underlying cardiac or pulmonary conditions are at higher risk of serious sequelae from RSV infection [4–6]. No effective treatment for RSV is approved for use; however, for high-risk children, palivizumab is approved for RSV immunoprophylaxis and is provided in monthly doses throughout the RSV season.

RSV emerges in seasonal circulation patterns with outbreaks occurring annually between September through May in most US regions. The onset/offset, month of peak activity, and duration of the season vary from year to year and among geographic regions [7–9]. RSV testing data, collected by the RSVAlert® surveillance program and by the U.S. Centers for Disease Control and Prevention (CDC) through the National Respiratory and Enteric Virus Surveillance System (NREVSS) [10,11], are used to monitor RSV seasons (Table 1). RSVAlert and the NREVSS are voluntary, laboratory-based surveillance networks that utilize RSV testing conducted during routine clinical care to monitor the circulation of RSV [10–14]. Whereas the NREVSS system is based on passive reporting, the RSVAlert program is based on active reporting of RSV testing from participating laboratories (ie, laboratories report weekly even when no testing occurred at their site and are

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Table 1
RSVAlert® program and NREVSS surveillance systems.

RSV surveillance system	RSVAlert	NREVSS[a]
Test reporting methodology	Active reporting	Passive reporting
Specimen test type covered		
Virus antigen	Yes	Yes
Virus isolation	Yes	Yes
PCR	Yes	Yes
Frequency of testing	Weekly	Weekly
Geographic circulation		
National	Yes	Yes
Census regional (4)	Yes	Yes
Division (9)	Yes	Yes
HHS regional (10)	Yes	Yes
State (core-based statistical area)	Yes	Yes

HHS, Health and Human Services; NREVSS, National Respiratory and Enteric Virus Surveillance System.
[a] NREVSS website: https://www.cdc.gov/surveillance/nrevss/.

reminded to report even if the deadline is missed). RSVAlert laboratories are recruited annually based on association with a large children's hospital and/or hospital with a neonatal and/or pediatric intensive care unit, a high volume of RSV tests reported in prior years (≥10 tests per week during RSV peak season) with good reporting compliance (ie, ≥70%), and/or geographic representation.

Accurately assessing RSV circulation in real time can help inform clinical care and efforts to reduce disease transmission; it is also essential to ensure optimal use of RSV immunoprophylaxis [11]. Traditionally, results of antigen-based RSV tests have been reported to the NREVSS to describe national RSV circulation [15]. The annual RSV season threshold has been defined as the time in weeks during which antigen-based tests detect RSV in > 10% of specimens [16,17]. Using this 10% threshold, the national RSV season has been shown to typically occur from fall through spring, but season onset varies among US regions [17].

The clinical context for PCR-based testing can differ from that of traditional RSV antigen testing, with PCR tests being more likely to be conducted in the inpatient setting and as part of a respiratory viral panel in patients with a lower pretest probability of having RSV disease. Midgley and colleagues assessed antigen and PCR-based RSV testing data submitted to the NREVSS during July 2005–June 2015 to understand the impact of RSV test type and positivity threshold on RSV season definition [10]. Midgley et al. found that the annual number of PCR-based reports increased 200-fold, whereas the number of antigen-based reports declined. The authors concluded that the traditional 10% positivity threshold for defining a season based on rapid antigen testing was not appropriate for PCR testing. Instead, three alternative approaches were found to be more appropriate for RSV season definition based on PCR test results. One was a threshold of 3% positivity (season onset as the first of 2 consecutive weeks when the weekly percentage of tests positive for RSV was > 3% and the last week that the percentage of tests positive for RSV was > 3%), which was considered useful for real-time surveillance. Two other methods, a retrospective slope 10 method and a 10-fold baseline method, also performed very well. However, these two methods required complex calculations and neither was considered appropriate for real-time RSV surveillance by local providers.

2. Objectives

The purpose of this analysis was to model implementation of the novel real-time PCR (3%) positivity threshold relative to the traditional antigen (10%) positivity threshold at national and regional levels using a large dataset of RSV testing results from participating RSVAlert laboratories during the 2011–2016 seasons.

3. Study design

3.1. Data collection

RSVAlert collects and reports information on routine RSV testing from approximately 480 hospital-affiliated laboratories across the United States [11–13]. Laboratory RSV test results (ie, virus antigen, virus isolation, or PCR) were submitted directly to and managed by IQVIA™ (Overland Park, KS, USA) weekly via fax, web reporting, or email; all data were deidentified before submission. Total tests and total positives were collected weekly from all participating sites and were aggregated at the local level.

A total of 599 laboratories participated in the RSVAlert program from 2011–2016. Seasonal collection of surveillance data began each August and continued through the following July. The data from all laboratories in the RSVAlert database were then compiled. Analysis focused on those laboratories that consistently reported data, defined as those that reported ≥10 tests for ≥30 weeks each season, to align with best practices [10,11] and avoid any potential confounding from laboratories intermittently providing data during a particular season.

3.2. Data analysis

National RSV test numbers and percent positivity were summarized by test type (antigen, virus isolation, and PCR) overall for each season and weekly within each season. Season onset and offset were calculated by test type. Data from each year were analyzed for seasonal trends at the national, regional, state, and local levels. For regional analyses, data

Table 2
Six Analytic Rules of RSV Seasonal Activity Using Antigenic and PCR Models.

Analytic Rules	RSV Seasonal Activity Definition	Reason for Modeling
Rule 1	> 10% positivity by antigen only	Traditional CDC-endorsed approach for real-time surveillance
Rule 2	> 3% by PCR only	Novel CDC-endorsed approach for real-time surveillance
Rule 3	The positivity threshold (10% for antigen or 3% for PCR) was exceeded for the predominant test type (the type with the greatest number of tests conducted) used in the specific geography during the season in question	One potential method to reconcile concurrent antigen and PCR data
Rule 4	The positivity threshold (10% for antigen or 3% for PCR) was exceeded for either test type	One potential method to reconcile concurrent antigen and PCR data
Rule 5	> 10% positivity by PCR only	Understand misapplication of antigen threshold to combined antigen/PCR testing
Rule 6	> 10% positivity by all tests reported (antigen and PCR)	Understand misapplication of antigen threshold to PCR testing

CDC, Centers for Disease Control and Prevention; RSV, respiratory syncytial virus.

Table 3
National RSV Test Counts and Percent Positivity by Season and Test Type: 2011–2016.

		Total RSV Tests		Antigen		Virus Isolation		PCR	
Season	# of Labs	Total Tests	% Positivity	Total Tests	% Positivity	Total Tests	% Positivity	Total Tests	% Positivity
2011–2012	209	463,453	**12.1%**	270,775	**15.7%**	70,445	**3.3%**	122,233	**9.0%**
2012–2013	212	610,444	**12.2%**	286,238	**16.7%**	70,033	**2.8%**	254,173	**9.7%**
2013–2014	215	466,638	**10.7%**	178,619	**15.5%**	34,384	**1.4%**	253,635	**8.6%**
2014–2015	188	586,595	**9.9%**	179,446	**15.0%**	28,375	**1.3%**	378,774	**8.2%**
2015–2016	184	589,806	**8.7%**	146,051	**14.1%**	21,087	**0.8%**	422,668	**7.2%**

RSV, respiratory syncytial virus.

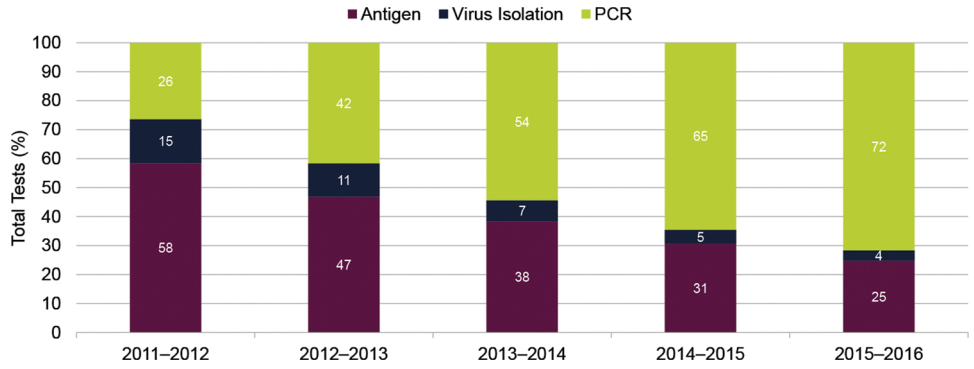

Fig. 1. Test type prevalence over 5 seasons.

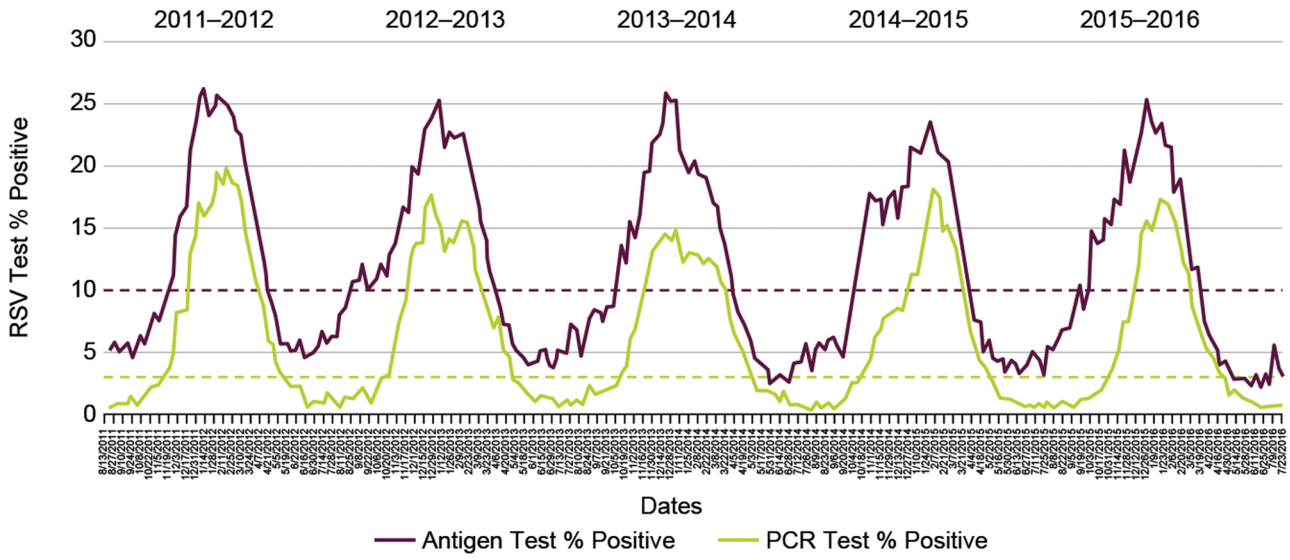

Fig. 2. Weekly RSV test percent positivity for antigen and PCR: 2011–2016. The dashed lines at 10% and 3% represent the 10% positivity antigen threshold and the 3% positivity PCR threshold, respectively. RSV, respiratory syncytial virus.

were stratified by the 10 regions defined by the U.S. Department of Health and Human Services (HHS). The New York HHS region was examined with the exclusion of data from Puerto Rico due to its atypical RSV epidemiology. All data from Puerto Rico were included in a local level analysis. To examine RSV seasonality at local levels, data were analyzed for a sample of 11 states including Hawaii, 20 core-based statistical areas (CBSAs), and substate regions within 5 states. CBSAs consist of metropolitan (urban core of ≥50,000 people) and micropolitan (urban core of ≥10,000 to < 50,000 people) statistical areas as defined by the U.S. Office of Management and Budget. Substate regions were identified within large states with significant geographic variability and enough laboratories to support separate analyses, specifically California, Florida, New York, Ohio, and Texas.

Onset-offset timing for 5 seasons (2011–2012 through 2015–2016)

Table 4
National and Regional Season Duration Estimates[a] Based on Analytic Rules.

National RSV Season	> 10% Positivity by Antigen (Rule 1)	> 3% by PCR (Rule 2)	Rule 1 or 2 Based on Predominant Test Type (Rule 3)	Either > 10% by Antigen OR > 3% by PCR (Rule 4)	> 10% by PCR (Rule 5)	> 10% by All Tests Reported (Rule 6)
2011–2012	21	26	21	26	15	19
2012–2013	32	27	32	35	17	20
2013–2014	26	29	29	30	18	20
2014–2015	25	28	28	30	12	19
2015–2016	25	26	26	31	12	15
HHS Region						
Boston	6–16	9–22	6–22	*Not analyzed*		
New York	15–19	22–25	19–25			
Philadelphia	18–26	21–26	21–26			
Atlanta	18–31	28–34	28–32			
Chicago	18–22	24–26	24–26			
Dallas	19–23	20–28	19–28			
Kansas City	16–20	8–26	16–26			
Denver	14–18	8–20	17–20			
San Francisco	19–30	16–31	19–30			
Seattle	14–21	12–20	17–21			

HHS, US Department of Health and Human Services; RSV, respiratory syncytial virus.
[a] Season durations and duration range estimates were in weeks.

were captured using the following categories: onset, the first of 2 consecutive weeks when ≥11 tests had a positivity above the relevant threshold for test type; and offset, the last of 2 consecutive weeks when ≥11 tests had a positivity above the relevant threshold for test type [13]. Given the concurrent use of antigen and PCR testing, 4 analytic rules were modeled to examine the optimal approach to determining RSV seasonality (rules 1 through 4, Table 2). The effectiveness of the various models was evaluated qualitatively based on the resulting RSV season durations, with outlier (excessively shortened or lengthened) estimates of season length being a marker of poor rule performance. Rules 5 and 6 were modeled to examine the effects of potential misapplication of RSV seasonality thresholds, specifically applying the 10% threshold to PCR-only test data or all test data. Rule 4 modeled the application of either criterion. Due to rules 4 through 6 resulting in overly narrow or broad RSV season definitions, only rules 1 through 3 were carried forward to modeling at the regional level. Rules 1 through 3 were evaluated as before, based on the resulting RSV season durations with a focus on outlier estimates, with the hypothesis being that rule 3 would perform best across geographies given variability in the test type utilized. As a result, rules were compared to determine whether there were instances in which rules 1 or 2 performed better than rule 3.

4. Results

4.1. National data

A total of 237 laboratories provided consistent weekly data (≥10 tests for ≥30 weeks of a season). Among these laboratories, an average of 543,387 RSV tests were reported each season, and PCR testing steadily increased in prevalence from 26% in 2011–2012 to 72% in 2015–2016 (Table 3, Fig. 1). Overall percent positivity differed by test type: 15.6% for antigen, 2.4% for virus isolation, and 8.3% for PCR, with trends toward lower positivity in later seasons.

National RSV season onsets and offsets were generally comparable using 10% antigen positivity and 3% PCR positivity for all seasons, although PCR-defined season onsets and offsets were often a few weeks later than antigen-defined seasons (Fig. 2). In 3 of 5 seasons, there was a larger difference in antigen versus PCR positivity early in the seasons.

We modeled 6 analytic rules for national RSV onset-offset duration across the 2011–2016 seasons (Tables 2 and 4, Fig. 3). The > 10% positivity by antigen approach (rule 1) yielded season durations of 21–32 weeks; the > 3% by PCR approach (rule 2) yielded 26–29 weeks; whereas the either > 10% by antigen or > 3% by PCR approach (rule 4) yielded 26–35 weeks. Onset-offset based on the predominant test type (rule 3) yielded season durations of 21–32 weeks. As expected, the > 10% PCR approach (rule 5) and > 10% by all tests reported approach (antigen and PCR) (rule 6) yielded shortened season durations.

4.2. Regional data

Season duration estimates were collected for regional laboratories that provided consistent RSV onset-offset for 5 seasons (Table 4, Fig. 4). In several instances, rules based on a low number of tests resulted in outlier estimates of shortened seasons, dramatically in some cases (Boston, Kansas City, and Denver) (Table 4). In 5 regions (New York, Philadelphia, Atlanta, Chicago, and Dallas), all rules provided robust results with no outlier season estimates. In 4 regions (Kansas City, Denver, San Francisco, and Seattle), the predominant approach provided the fewest outlier season estimates, which in some cases was equivalent to other rules when the predominant test type did not change across seasons or when rules provided similar results. In one region (Boston), PCR provided fewer outlier estimates than the predominant rule, driven by an anomalously short season determined by antigen testing in the 2012–2013 season.

4.3. State and substate data

Onset-offset duration estimates of 5 RSV seasons for the top 10 states plus Hawaii by test type are shown in Fig. 5. The predominant approach was equivalent to the antigen rule as antigen testing was predominant in all seasons. In 9 states (California, Illinois, Michigan, Missouri, New York, Ohio, Pennsylvania, Texas, and Washington), all rules provided robust results with no outlier season estimates.

Regions were broken down into top 20 CBSAs (Fig. 6). Criteria were

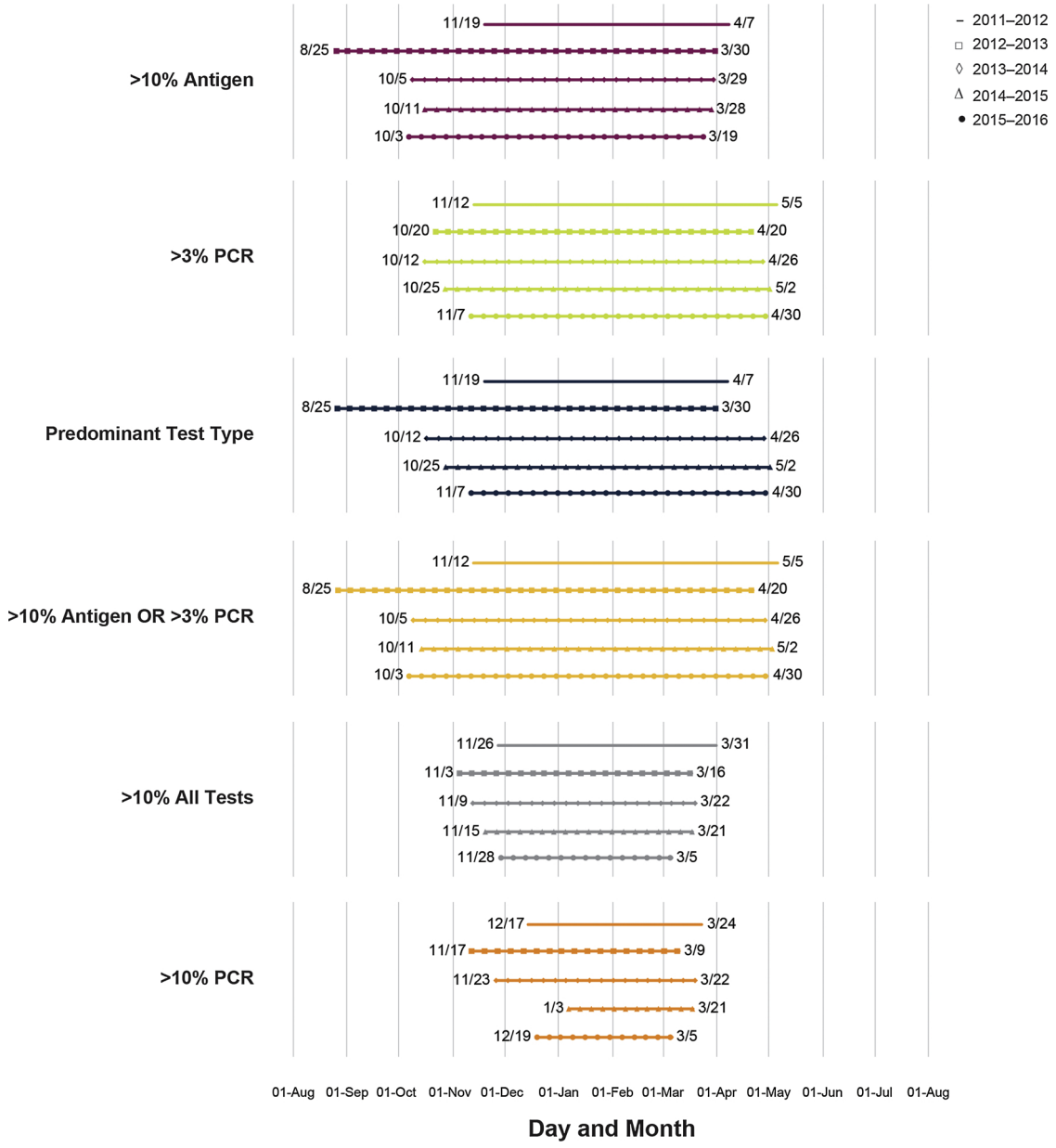

Fig. 3. National RSV season onset and offset by analytic rule: 2011–2016. RSV, respiratory syncytial virus.

not always met by either antigen or PCR test types, but the predominant approach provided reliable season estimates in all CBSAs. Similarly, for subregions of 5 states (Fig. 7), the predominant approach provided reliable season estimates in all geographies.

5. Discussion

In recent seasons, PCR testing for RSV has increased considerably, whereas virus antigen and virus isolation testing have decreased. We have shown that RSV positivity differs by RSV test type, likely due to PCR panel testing for respiratory illnesses resulting in more RSV tests being conducted on patients with a lower probability of having RSV disease. Our analyses confirm the results of the recent CDC analysis that showed that PCR positivity of 3% appears comparable at the national level to the traditional antigen positivity threshold of 10% [10]. In addition, our analysis extends those findings to the regional and local levels, and also demonstrates that real-time decisions regarding RSV activity may be most robust when based on the predominant test type utilized in the regional or local geography. This approach avoids misleading estimates that can result from small test numbers.

Increasing use of PCR testing was first noted in a 2013 analysis that described changes over time in the type of tests used for primary RSV detection by US hospital-affiliated laboratories [14]. PCR tests accounted for 2%, 3%, 16%, and 21% of weekly tests (total range, 381,068–481,654 over 4 seasons), respectively, conducted each season from to 2007–2008 through 2010–2011. The current results and those

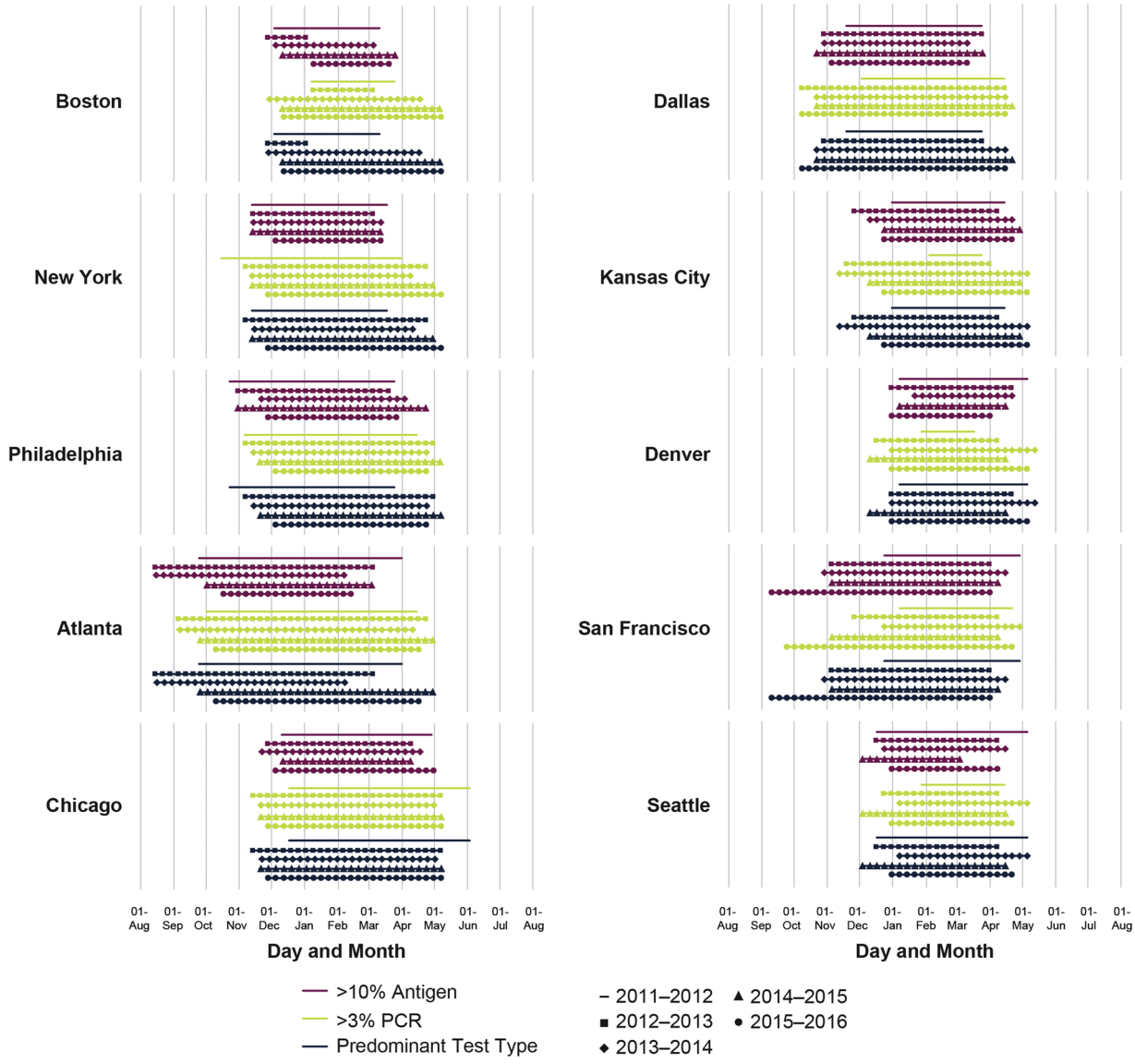

Fig. 4. RSV season onset and offset by HHS region and analytic rule: 2011–2016. HHS, U.S. Department of Health and Human Services; RSV, respiratory syncytial virus.

of Midgley et al. [10] make it clear that those trends have continued, with PCR testing becoming more prevalent than antigen testing in the 2013–2014 season. As a result, PCR-based reports are increasingly relevant for RSV surveillance and determining the seasonality of RSV. If prevalent in a specific geography, PCR-specific methods can provide a more comprehensive understanding of RSV activity. RSV surveillance systems relying solely on virus antigen testing results will not capture an increasing proportion of RSV test results.

Accurate season definition is particularly important for timing of RSV immunoprophylaxis, as noted by previous studies. Using data from 1999 to 2004, Hampp et al. found that > 10% positivity with antigen RSV test positivity correlated with RSV hospitalization risk in high-risk infants [18]. Glick et al. similarly correlated > 10% antigen positivity with RSV hospitalization incidence using data from 2010 to 2013 [19]. However, Glick et al. found that many RSV hospitalizations occurred before and after regional activity as defined by the > 10% antigen threshold. Mean RSV hospitalization season onset occurred 3 weeks before and 4 weeks after regional activity season onset based on antigen testing. Glick et al. also found that RSV immunoprophylaxis began in advance of the antigen-defined RSV season, which is important to ensure that antibody levels are established in high-risk infants prior to RSV exposure.

RSV PCR testing, often part of respiratory panel testing, is more likely to be conducted in the inpatient setting, and may be less susceptible to selection bias than antigen testing. PCR-based respiratory viral panel testing is often employed across age groups when a serious viral respiratory disease is suspected. In contrast, rapid antigen testing for RSV is utilized predominantly in children to confirm suspected RSV

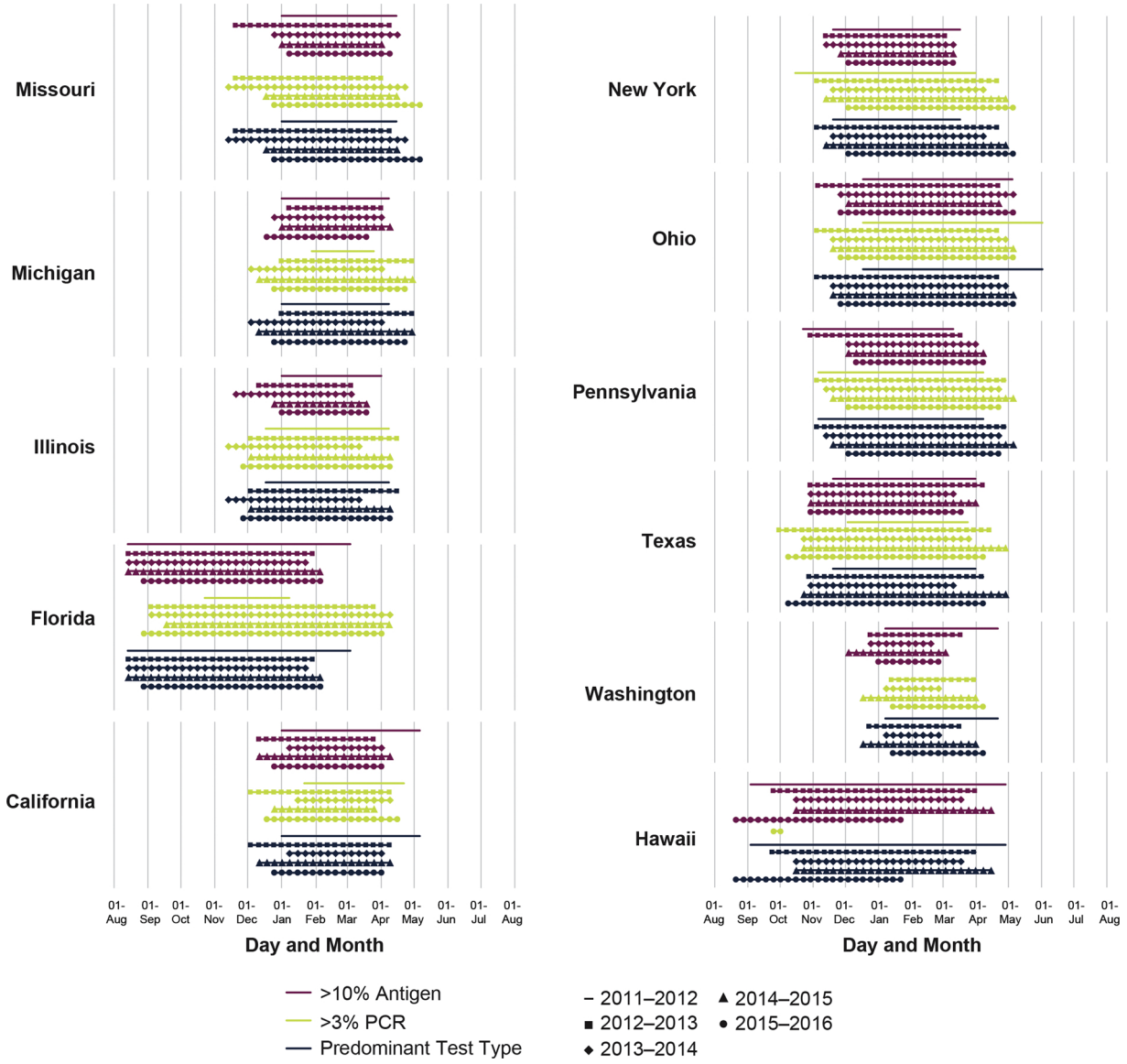

Fig. 5. RSV season onset and offset for 10 large states plus Hawaii by analytic rule: 2011–2016. In Florida, antigen onset occurred prior to the season definition start date for 4 of 5 seasons. PCR criteria were not met in Missouri and Washington for the 2011–2012 season. Hawaii did not meet PCR criteria at all in 4 seasons (2011–2015) and only met PCR criteria for 2 weeks in the 2015–2016 season. RSV, respiratory syncytial virus.

disease. As a result, antigen testing may be subject to selection bias with providers testing patients more likely to be positive and/or testing more frequently during certain months (eg, before and during the start of the RSV season) when RSV ascertainment can help elucidate the timing of the upcoming RSV epidemic. The increased inpatient use of PCR testing and/or the greater use of antigen testing in children may explain the higher early-season positivity and earlier season onset and offset we observed with antigen testing data. Unfortunately, we were not able to examine this difference further as no data were available on the patient characteristics associated with each test. Without a well-controlled study in which patients are tested simultaneously with both test types, precise comparisons and robust conclusions are not possible.

The current study and findings must be interpreted in the context of several limitations. The RSVAlert laboratories included in the analysis are a convenience sample, and RSV testing is not systematically conducted. As a result, these data may not fully represent US RSV circulation. It is reassuring that the results are generally similar to those reported by the CDC [10]. The data should not be affected by meaningful reporting bias, as participating laboratories were required to report results of all tests conducted. However, antigen and PCR testing use vary by geography, hospital, and clinical setting and may also vary across patient types. Comparisons of antigen and PCR testing using data derived from routine clinical testing of patients are not ideal, as observed differences may be due to differential clinical use of the test types. No data were collected regarding the patient characteristics associated with each test, so we could not perform any analyses

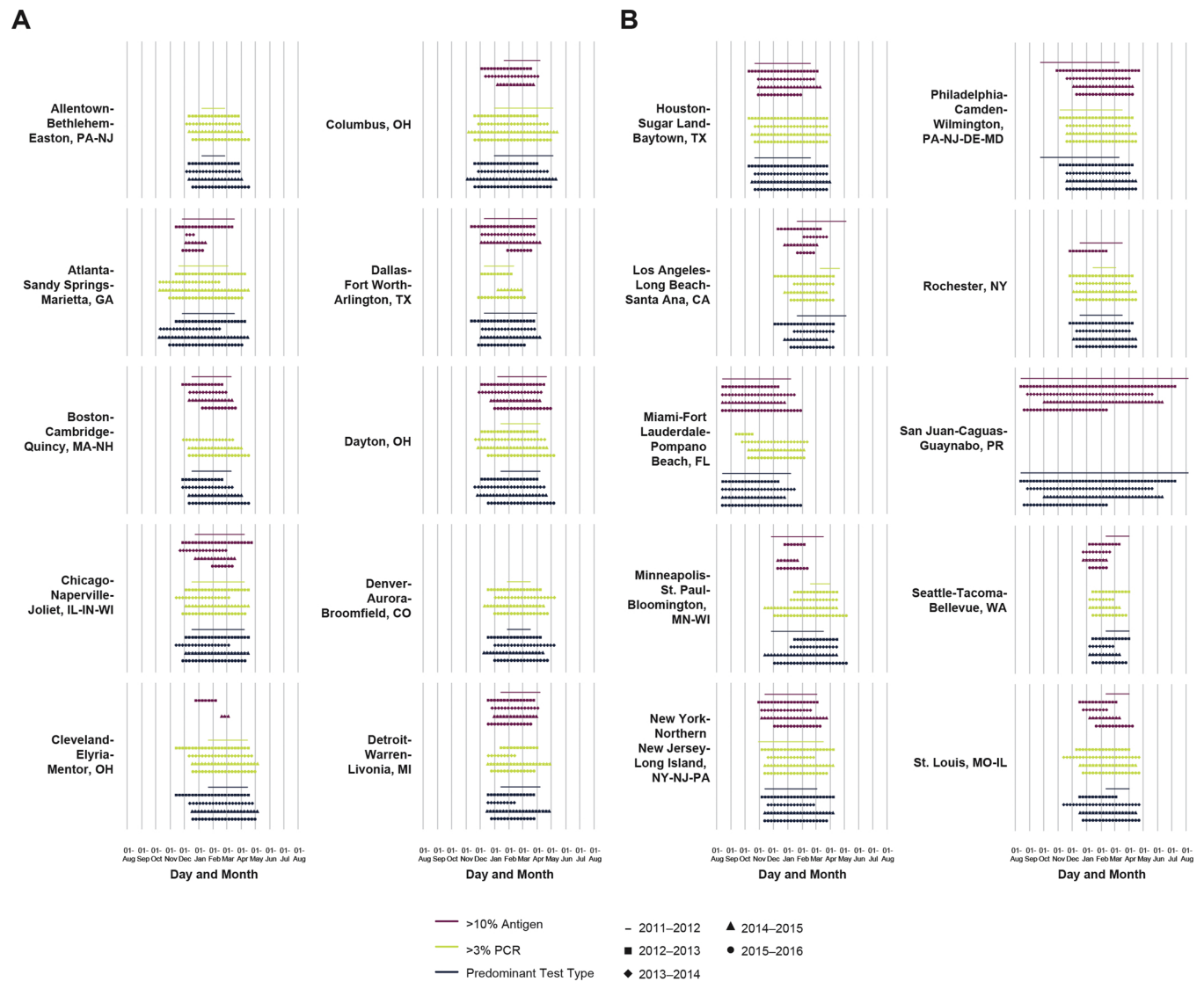

Fig. 6. A, B. RSV season onset and offset for 20 CBSAs by analytic rule: 2011–2016. In Miami and Puerto Rico, antigen onset occurred prior to the season definition start date for 4 of 5 and 2 of 5 seasons, respectively. CBSA, core-based statistical area; RSV, respiratory syncytial virus.

controlling or adjusting for patient characteristics.

In conclusion, RSV seasonality that is defined based on a test type positivity threshold can guide health care provider assessments of local activity and in turn inform clinical care, efforts to reduce disease transmission, and optimal use of RSV immunoprophylaxis for eligible high-risk infants and children.

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Ethical approval

Not required.

Transparency document

The Transparency document associated with this article can be found in the online version.

CRediT authorship contribution statement

Christopher S. Ambrose: Conceptualization, Data curation, Funding acquisition, Methodology, Project administration, Supervision, Visualization, Writing - original draft, Writing - review & editing. **Lisa L. Steed:** Resources, Writing - review & editing. **Mike Brandon:** Resources, Writing - review & editing. **Kara Frye:** Resources, Writing -

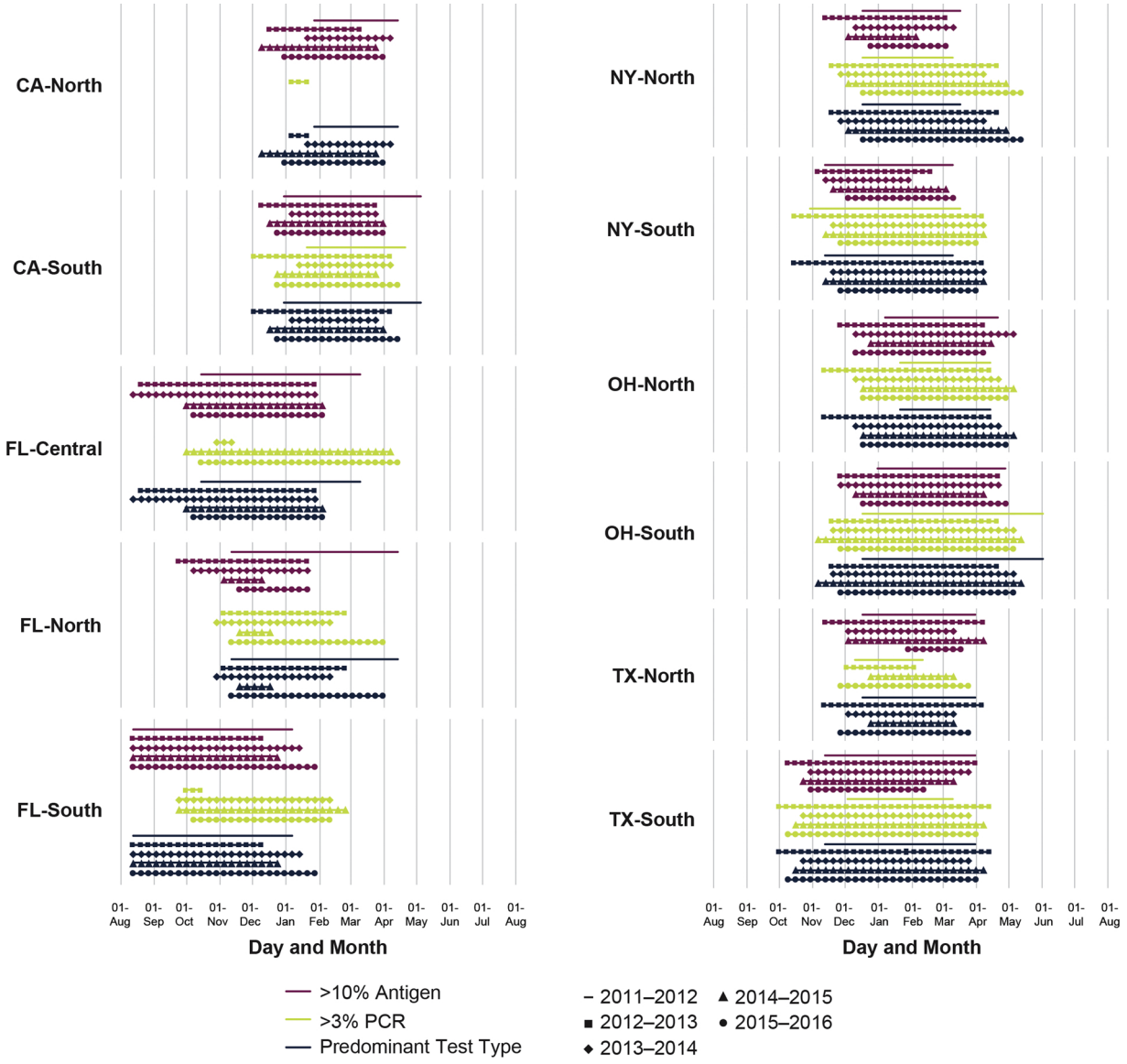

Fig. 7. RSV season onset and offset for substate regions by analytic rule: 2011–2016. California-North did not meet PCR criteria for 4 of 5 seasons and met PCR criteria for only 3 weeks during the 2012–2013 season. Florida-Central did not meet PCR criteria for the 2011–2012 and 2012–2013 seasons and met PCR criteria for only 3 weeks in the 2013–2014 season. Florida-North did not meet PCR criteria for the 2011–2012 season. In Florida-South, antigen onset occurred prior to the season definition start date and did not meet PCR criteria for the 2011–2012 season. Texas-North did not meet the PCR criteria during the 2013–2014 season. RSV, respiratory syncytial virus.

review & editing. **Ifedapo R. Olajide:** Conceptualization, Funding acquisition, Project administration, Writing - review & editing. **Gina Thomson:** Resources, Writing - review & editing.

Declaration of Competing Interest

LLS, MB, KF, and GT's institutions received compensation from IQVIA for participation in the RSVAlert program, which is supported by AstraZeneca. CSA and IRO are employees of AstraZeneca.

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