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Factors Influencing Consistency of Laboratory Reporting in Surveillance of Respiratory Syncytial Virus

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ABSTRACT

Factors Influencing Consistency of Laboratory Reporting in Surveillance of Respiratory Syncytial Virus

By Sara Demas

Background: Respiratory Syncytial Virus (RSV) is the leading cause of viral lower respiratory tract infections in young children in both developed and developing countries, with almost 34 million new cases occurring worldwide each year. Comprehensive and well-timed information on RSV characteristics is essential for determining seasonality, burden of disease, and effective prevention and control measures. The objective of this thesis is to examine the factors that affect consistency of RSV reporting to NREVSS.

Methods: Using data from the National Respiratory and Enteric Virus Surveillance System between 2003 and 2013 and a standardized laboratory assessment, analysis of variance and a logistical regression model were performed to study the association between the outcome, consistent reporting, and exposure variable, mode of reporting, adjusting for laboratory locale, testing protocols and diagnostic test used.

Results: Data collected from 884 participating laboratories reported a total of 4,989,768 RSV tests for the sum period of 188,994 lab weeks. Mode of reporting (direct vs. indirect), regional location, and diagnostics methods (antigen, PCR, and culture) were all factors significantly associated with consistent reporting. Among the subset of assessed laboratories, year round testing and selection of testing methods were also found to be significant modifiers in consistent reporting.

Conclusion: Laboratories that were direct reporters, located in the Southern region, and used antigen detection had greater odds of reporting consistently to NREVSS. Of the subset of assessed laboratories, reporting year round and using a standard protocol for selection of testing methods also increases odds of consistent reporting. This study suggests direct reporting and testing methods are good measures of reporting consistency and allow for more representative data on RSV circulation.

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TABLE OF CONTENTS

BACKGROUND/INTRODUCTION

Respiratory Syncytial Virus

Respiratory Syncytial Virus (RSV), a negative-sense single-stranded RNA virus of the family Paramyxoviridae, is the leading cause of viral lower respiratory tract infections among infants and young children in both developed and developing countries, with almost 34 million new cases occurring worldwide each year (Javed Akhter, 2011) (Mejias & Ramilo, 2013). Most infants are infected in the first year of life, and nearly all children will have been infected by two years of age (Javed Akhter, 2011). RSV is the largest single cause of childhood hospitalizations due to lower respiratory disease. In the United States, an estimated 100,000 infant hospitalizations and 4500 deaths among infants diagnosed with RSV occur annually due to RSV infections (Stockman, Curns, Anderson, & Fischer-Langley, 2012). RSV also contributes to an increased number of emergency department and pediatric practice visits (Hall et al., 2009). When compared to RSV hospitalizations, rates of RSV visits were found to be 9 times higher among emergency department patients and 26 times higher among private practice patients (Hall et al., 2009). Combined direct medical care and health resource costs associated with RSV related illness in the US have estimated an annual economic burden of $652 million USD annually (Paramore, Ciuryla, Ciesla, & Liu, 2004) .

At present, there is no USDA approved vaccine in the US for RSV. However, immunoprophylaxis through the administration of palivizumab (Synagis) has been shown to reduce morbidity and mortality among infants and young children at high risk for severe RSV diseases (Feltes & Sondheimer, 2007; Marchetti, Lau, Magar, Wang, & Devercelli, 1999; Shireman & Braman, 2002; Singleton, Dooley, Bruden, Raelson, & Butler, 2003). Study finding

have suggested use of palivizumab has led to a 55% reduction in RSV hospitalizations (Group, 1998). Based on study findings, the cost of prophylaxis for 1 RSV season is calculated to be $6,160 per patient (Yount & Mahle, 2004). Considering the high cost of injection, the American Academy of Pediatrics (AAP) recommends limiting the administration of palivizumab to coincide with peak RSV outbreak in a given community (Armstrong, 2010).

In the United States, RSV season typically occurs begins in late fall and ends in early spring, with variable onset, peak activity, and duration (Control & Prevention, 2011). Trends within the United States reflect peak RSV activity between November and March and lasting between 13-20 weeks. Since RSV seasonality varies from region to region, AAP cites data from the Center for Disease Control and Prevention (CDC) as an indicator of RSV onset and offset in different geographic locations in the United States (Armstrong, 2010; Control & Prevention, 2011).

NREVSS

Since 1989 the Centers for Disease Control and Prevention (CDC) established a national, laboratory-based passive surveillance system called the National Respiratory and Enteric Virus Surveillance System (NREVSS) (http://www.cdc.gov/surveillance/nrevss/rsv/default.html) to collect data in monitoring RSV activity, as well as other additional respiratory and enteric viruses. NREVSS tracks laboratory detections of RSV and other respiratory and enteric viruses and serves as an indicator of seasonal trends in the U.S. Each week, participating laboratories report weekly aggregate RSV tests and positive detection, by test type, to NREVSS. State and local public health providers use NREVSS data to determine timing of RSV at the national, state, and local level. Given the variations of RSV occurrence in the United States, NREVSS assists in exploring how RSV occurence vary by areas and potential factors influencing this trend. The

NREVSS is a key tool in determining the onset of RSV season in communities. Because of its major role in identifying the onset of the RSV season, it is also helpful in narrowing the optimal timing of the administration of the immunoprophylaxis (Catherine A Panozzo, Stockman, Curns, & Anderson, 2010).

The lack of an effective vaccine for RSV further reinforces the importance of surveillance of RSV to prevent transmissions and reduce hospitalizations. NREVSS surveillance can be utilized for planning care and costs and monitoring of outbreaks. Early detection of RSV outbreaks enhances the capacity to signal an increase in hospital staffing and medical supplies to provide timely intake, assessment, and treatment for potential RSV patients. Efficient infection control reduces outbreak intensity, decreases illness severity for high risk populations, and reduce overall healthcare expenditures. Although RSV vaccine development is in progress, surveillance system enhancement is considered a priority (Graham, 2014; Guvenel, Chiu, & Openshaw, 2014). NREVSS is a simple surveillance estimating disease burden that allows for low cost and burden to reporter, which is critical to vaccine development and future evaluations of RSV vaccine effectiveness (Anderson et al., 2013).

In addition to understanding RSV prevalence, NREVSS is useful in tracking laboratory advancements. Laboratory diagnostics play a vital role in the diagnosis of respiratory virus infections and timely interventions. RSV can be detected by three different diagnostic methods: antigen detection, polymerase chain reaction (PCR), and culture (viral isolation). Given the clinical similarities of RSV infections to that of influenza and human metapneumovirus, laboratory confirmation provides a quantitative diagnosis of infection (Mahony et al., 2007; Manoha, Espinosa, Aho, Huet, & Pothier, 2007). Since laboratories may use differing diagnostic

methods, NREVSS also shows elucidative records in laboratory testing (Rabon-Stith et al., 2013).

Comprehensive and well-timed information on RSV characteristics is essential for understanding seasonality, disease burden, and detection of potential outbreaks, as well as the development of future prevention strategies. Given the significant application of RSV surveillance, the information being reported to NREVSS has many implications for its usefulness. Therefore, quality and useful RSV surveillance is essential to effectively support the public health research and interventions for RSV.

Surveillance

As the cornerstone of public health practice, surveillance activities are important for the detection and understanding of disease epidemiology to help control or address health problems (Thacker, Parrish, & Trowbridge, 1988). For respiratory viruses, surveillance has been used in understanding disease etiology, monitoring seasonality, detection of outbreaks, as well as estimating the burden of infection, morbidity and mortality (McGuiness et al., 2014; Stockman et al., 2012; Thompson, Shay, Weintraub, & et al., 2003). Surveillance data has also informed vaccination policies for vaccine preventable respiratory viruses, such as influenza virus (Greene et al., 2012). Ongoing monitoring and surveillance of identifiable respiratory viruses is important for disease management and minimizing community impact.

Since 1878, when Congress first authorized the collection of disease associated morbidity data, the diseases under surveillance and data collection methodology have evolved (Thacker, Choi, & Brachman, 1983). Considering the advancements and the importance of surveillance in informing public health practice, CDC developed guidelines to evaluate surveillance systems in

1988, with the most recent supplement update in 2001 (German et al., 2001). These guidelines ensure public health problems are monitored efficiently and effectively (German et al., 2001). More generally, surveillance guidelines necessitate regular evaluation of quality and usefulness of data from public health surveillance systems.

Surveillance evaluation initiates systematic review of platforms ability to meet its purpose and objectives, also known as its usefulness. There are nine attributes recommended for measuring a surveillance system's usefulness: simplicity, flexibility, data quality, acceptability, sensitivity, predictive value positive, representativeness, timeliness, and stability (German et al., 2001). Although characteristics important to surveillance systems may vary depending on the systems objectives and functions, execution of these nine attributes determine the usefulness and cost of a surveillance system.

For the purpose of this analysis, data quality was found to be the most relevant measure of assessment for RSV NREVSS data. Data quality can be seen as the completeness and validity of the data obtained in the surveillance system (German et al., 2001).

Data Quality

As discussed above, representativeness and data quality are two of the nine measures in evaluating surveillance systems usefulness and have also been the most common criticisms of passive surveillance systems versus active surveillance (Kimball, Thacker, & Levy, 1980; Catherine A. Panozzo, Fowlkes, & Anderson, 2007; Thacker et al., 1983). Complete and accurate reporting depends on many factors, such as reporting source, timeliness of investigation, and completeness of data (Sandra Roush). Many variables influence data quality and data representation. Only a handful of studies have published assessment of complete and accurate surveillance reporting (Armour, Nguyen, Lutman, & Middaugh, 2013; Hampp et al., 2013).

Lab practices and procedures are two components previously utilized as a proxy for reporting accuracy in laboratory based platforms. Previous research has quantified the impact of laboratory practices and testing methods on surveillance quality of data (Atchison et al., 2009; Fox, 2007). Atchison et al. investigated diagnostic tests used, testing indicators, policies, and changes to testing policies in participating labs surveillance. These studies concluded that only a fraction of community cases are reported to national surveillance system and site reporting practices, criteria for testing, and the diagnostic methods as the primary drivers of bias observed in lab-based surveillance.

Studies have also reflected that nucleic amplification tests (NATS) detect primarily idiopathic respiratory cases, as antigen was primary testing when primary population was children. PCR is now the most common diagnostic method reported to NREVSS. Recent studies reflect an increase in the number of PCR tests conducted and the number of laboratories performing PCR testing among US hospital affiliated laboratories (Rabon-Stith, 2013).

The objective of this thesis is to examine the factors that may affect the consistency and volume of RSV submitted to NREVSS. By exploring factors such as the type of laboratory affiliation, laboratory locale, testing protocols and diagnostic test used, we analyze the influence of these factors on the completeness and timeliness of RSV reporting to NREVSS. Understanding the effect of laboratory recruitment and testing practices on national data is fundamental to understanding the extent to which patterns observed in surveillance data reflects underlying regional trends. This study will provide a quantitative evaluation of improvements to comprehensive reporting of RSV surveillance in the United States.

Program management and policy development critically depend on the quality of surveillance data. If the information gathered is faulty, programs designed to control disease,

cannot appropriately recommend treatment and prevention, and will be incapable of effectively monitoring trends.

Research questions/Null Hypothesis

These are two questions of interest:

1. What is the effect of direct reporting (vs. indirect) on national RSV reporting rates in the United States?
    - Null hypothesis: Mode of reporting does not have a significant effect on consistent reporting

2. What is the effect of laboratory practices on national RSV reporting rates in the United States?
    - Null hypothesis: Laboratory practices does not have a significant effect on consistent reporting

METHODS

Description of NREVSS

NREVSS is a laboratory-based surveillance system consisting of a network of private, university, and community hospitals, research institutions, commercial and reference laboratories, and health clinics located throughout the United States. NREVSS collects data on numerous respiratory and enteric viruses, which include respiratory syncytial virus (RSV), influenza, rotavirus, human parainfluenza virus (HPIV), human metapneumovirus (hMPV), adenoviruses, and enterovirus. Participating laboratories submit weekly aggregates of tests performed and positive results for RSV in the NREVSS Online Data Submission System (ODSS) website. The data is stored in a SQL data which can be viewed and analyzed in Microsoft Access. The Centers for Disease Control and Prevention writes annual reports for three test types: antigen, detection, culture, and PCR, which can be accessed at http://www.cdc.gov/surveillance/nrevss/rsv/default.html.

In order to answer our research questions, we performed a study on all labs and a second study on a subset of assessed labs. Both were retrospective studies of reporting consistency among laboratories reporting RSV to NREVSS, a surveillance program funded by CDC National Center for Immunization and Respiratory Diseases (NCIRD) Division of Viral Diseases (DVD). The main outcome of interest was RSV reporting consistency, as determined by number of weeks reported during specified season. Consistent reporting was defined as reporting at least 36 (out of 52) weeks in a given season. Inconsistent reporting was laboratories reporting less than 36 weeks. The main predictor of interest was mode of reporting, direct vs. indirect reporters. Additional independent predictors also considered in each study.

We did this to study understand which factors were important predictors of the outcome, consistent reporting.

Analysis of all labs

For the purpose of all labs study, we extracted RSV detection reported to NREVSS from September 2003 through August 2013. Laboratories were located in the four census regions established by U.S. Census Bureau (listed in Table 1). Testing practices and laboratory procedures depend on institutional protocols and physician ordering practice. No standardization was applied to population tested or diagnostic tests performed by each reporting laboratory.

Analysis was limited to data reported for at least 1 RSV test performed per week during the study period to provide a standard period and allow for comparison between data reported directly to CDC and those reported through a third party to the CDC; IMS Health. From Sept. 2010 to Aug. 2013, a data sharing agreement was established with IMS Health (formerly SDI health). Prior to then, between the periods of Sept. 2006- Aug. 2009, a memorandum of understanding was established between CDC and third party. Indirect reporters were defined as laboratories reporting through contractual agreement with IMS health for the period defined above.

We used analysis of variance to investigate whether certain mode of reporting, regional location, and diagnostic methods selected were associated with a greater consistency in reporting. Multivariate analyses assessing the association of consistent reporting with mode of reporting adjusting for diagnostic methods and regional were conducted using logistic regression. We also performed a backward elimination on multivariable models with interaction terms to identify potential effect modification (at significance level $p<0.05$). Consistent reporting was

defined as laboratories reporting at least 36 (out of 52) weeks in a given season. We excluded records with missing values or responses coded as “don’t know” or “refused to answer”. The statistical evaluation used logistic regression to yield odds ratios (ORs) to assess the relationship between consistent reporting and reporting type.

Analysis of surveyed labs

From Jan. through Feb. 2014, 50 laboratories were assessed using a structured questionnaire administered by myself and NREVSS staff to available, voluntary laboratory supervisors and managers in each of the laboratories. Laboratories were selected by convenience sampling of laboratories recommended as critical reporting laboratories for NREVSS and which data has been used to inform RSV trend in the United States. Sites were contacted via telephone using laboratory contact profiles recorded in the NREVSS database and the assessment averaged 10-15 minutes. The lab assessment inquired demographics, testing procedures, data recording and reporting practices. Questions including the following:

- Year-round testing
- Protocol for selecting testing methods
- Changes in protocol/testing procedures between on and off season

Responses were compiled in Microsoft Access database and pooled with test reporting data for analysis.

We assess the impact of the mode of reporting, diagnostic methods, regional location, and assessed laboratory testing practices on consistent reporting by fitting a logistical regression model to estimate whether the consistency in reporting was associated with the mode of reporting adjusting for additional predictors. For subset analysis, we also considered whether laboratories tested for RSV year-round, using a standard protocol, physician’s order, or both in the selection of testing methods, and if laboratory’s testing practices changed between on and off

season. We excluded records with missing values or responses coded as “don’t know” or “refused to answer”. The statistical evaluation used logistic regression to yield odds ratios (ORs) to assess the relationship between consistent reporting and reporting type.

All analyses were done by using the SAS software system (Version 9.3, SAS Institute, Cary, NC).

RESULTS

Descriptive Characteristics

Descriptive characteristics of NREVSS laboratories by consistent reporting and volume of RSV tests are shown in Table 1. Overall, we collected data from 884 participating laboratories in 50 states, including DC, using NREVSS. A total of 4,989,768 RSV tests were reported in the United States between 2003 and 2013, for the sum period of 188,994 lab weeks. The bulk of laboratories were indirect reporters (794/884) and the highest participation for laboratories in NREVSS was between the 2006- 2010 period (825/884). Laboratories located in the South made up the majority of all labs in NREVSS totaling 38.68%, with Midwest following at 24.3%.

When stratifying the groups of laboratories by diagnostic methods, antigen testing was the most common diagnostic method utilized, encompassed 63.3% of all RSV tests reported during this surveillance period which culture and PCR made up 20.8% and 15.9% respectively. In the most recent contract period, 2010-2013, the number of RSV tests reported for PCR doubles from 208,433 to 582,354, while volumes for both antigen and culture diagnostic volume have decreased. As can be seen in the 2012-2013 season (Table 3), PCR testing has a median of 1594.5 RSV tests per season, while antigen and culture have 324.00 and 429.00 respectively.

Laboratories reported RSV tests for a median of 38 weeks annually (Table 1c). When stratified into diagnostic methods, RSV reporting using culture is the most consistently reported diagnostic methods, with a median of 44.00 weeks per season reported (compared to 40 weeks for antigen and 41 for PCR). Although laboratories reporting culture may have decreased volume in recent years, culture reporting is consistent. However, Table 3 reveals PCR reporting consistency is continuing to rise as shown in most recent reporting of 45 weeks in 2012-2013

season.

During 2012-2013 season, 501 laboratories participated in NREVSS, reporting a median 367 RSV tests and median of 43 weeks. Reporting trends varied by season, with RSV reporting consistency peaking during the 2005-2006 season with laboratory recording a median of 1144 RSV tests and a median of 49 weeks. The RSV reports in NREVSS increased dramatically from 2006-2007 (Table 2). This sudden increase coincides with the increase in laboratories reporting to NREVSS between the 2006-2007 season and 2007-2008 season. Although the number of laboratories and RSV reports have increased during this time, the median volume of tests and number of weeks that a laboratory reported decreased from 48 weeks (prior to 2006) to 36 weeks in the 2007-2008 season. This reflects that although there may have been an increase in laboratories reporting to NREVSS, these laboratories may have been more unpredictable. Recent years reflect an increase in reporting regularity and volume.

The number of RSV tests using PCR reported has also increased dramatically over the years with the absence of PCR testing in 2003-2004 season to a median of 1594.5 tests reported in 2012-2013 season. This also aligns with the increasing consistent in reporting of PCR in recent years.

Subset of Laboratories

Fifty of 884 (5.65%) microbiology laboratories in the US completed the laboratory assessment. Descriptive characteristics for subset of assessed laboratories are presented in Table 1. Compared to the population of 884 laboratories, a smaller proportion of labs from the subset were located in the southern region. However, subset labs were more consistent reporters (median rates) and reported larger amount of RSV tests relative to the overall population of

NREVSS laboratories. 27.1% of all lab tests were reported by this subset of 50 labs and were reported at an overall median rate of 52 weeks per season. From 2003 through 2013, a total of 1,351,771 RSV tests were reported by these 50 laboratories for the period which account for a total of 28,613 lab weeks. Considering these labs were identified as critical laboratories for monitoring RSV trends, these finding support such.

Each subset lab used antigen testing, with culture as the second most common. Approximately half of the 50 labs use culture or PCR. Similar to the total population, laboratories reporting culture and PCR are the more consistent reporters, reporting a median of 52 weeks per season (Antigen reports median of 50). Also similar to results in total population, PCR reporting has continued to increase with each subsequent season, approximating a little less than half of antigen tests reported in the 2010-2013 contract period.

Assessment of Lab Practices and Testing

The results from the laboratory assessment revealed that 92% (46/50) of laboratories routinely tested for RSV year-round with the exception of 4 laboratories, in which 2 reported testing for RSV only during the winter season (Table 2).

28 % (15/50) of laboratories replied "yes" to changing testing practices for RSV between on and off season. Most of these changes in testing practices were associated with variations in diagnostic methods used. When stratified by reporter type, there is a significant difference for testing practices for RSV between on and off season for direct and indirect reporters ($p<0.0001$).

Laboratories were evaluated on the selection of diagnostic methods used. A similar proportion of laboratories reported using standard protocol only and physician order only (44% and 40% respectively). Only 16% of laboratories indicated using a standard protocol and

physician's order in selecting diagnostic methods. When stratified by reporter type, there was a significant difference in the selection of diagnostic methods among direct and indirect reporters (*p=0.0264*). Direct reporters were more likely (50%) to utilize only physician's order while indirect reporters were more likely to utilize a standard protocol only.

Analysis

All labs

In the bivariate analysis, reporter type (direct vs. indirect) was significantly associated with consistency in reporting (*p<0.0001*). There were 2.88 increased odds of reporting consistently among direct reporters than indirect reporters. The analysis also showed that regional location of laboratories was also significantly associated with reporting consistency. Laboratories located in the Northeast region were more likely not to report consistently than laboratories in the Midwest, South, and West (*p<0.0001*). Laboratory RSV detection by culture had a 1.20 increased odd to consistently report compared to labs reporting RSV by antigen detection, while reporting for PCR had 0.884 decreased odds for consistent reporting in relation to antigen (*p=0.0105*). Reporting consistency was the most high between 2003-2006. The period of reporting with the least odds of reporting consistency were 2006-2010 (β=0.261) and 2010-2013 (β=0.410) (*p<0.0001*).

Regional location, contract period, and test type were all statistically significant effect modifiers of the relationship between reporter type and consistent reporting. After stratification, a significant interaction was observed among regional location, contract period, and test type; these interactions were included in the final model. The final model included reporter type, region, test type, and the interaction between reporter type and region, and reporter type and test

type (Table 3).

Subset Labs

Bivariate analysis for the subset of laboratories also revealed a strong association with reporter type and consistency (*p=0.0003*). Similar to analysis of all labs, laboratories in the Northeast were significantly less likely to consistently report than Midwest, South, and West regions (*p=0.0408*). Compared to 2003-2006 contract period, there was a 0.383 decreased odds of consistent reporting during 2006-2010 contract period, and 0.440 times increased odds during 2010-2013 contract period (*p=0.0095*). Applying the responses from the assessment, both testing for RSV year round (*p=0.0415*) and method for selection of testing methods (*p=0.0269*) were associated with consistent reporting. Laboratories which tested year round had 1.745 times greater odds of reporting consistently. The use of a standard protocol in selecting the testing method also increased the likelihood of consistent reporting. Conversely, changes in testing practices between on and off season were not correlated with consistent reporting (*p=0.1565*). Also, test type was not significantly associated with consistent reporting.

Our multivariate analysis found regional location and selection of testing method as important effect modifiers for the outcome of consistent reporting. After stratification on regional location and selecting of testing method a meaningful interaction continued to be appreciated. The final model included reporter type, regional location, test type, year round RSV testing, selection of testing methods, as well as the interaction of reporter type and region and reporter type and selection of testing methods. Contract period was the only factor not included in the multivariate model given the lack of significance in the multivariate analysis.

DISCUSSION

Surveillance serves as a key component in monitoring disease and assessing public health (Caliendo et al., 2013). RSV surveillance is particularly important to managing burden of disease and tracking epidemic pattern of RSV. Laboratory surveillance, in particular, reduces the risk of hospitalizations by guiding human resource allocation, prevention messages, and informing infection control to prepare for prophylaxis administration. Systematic review of laboratories, which may vary by region, testing methods, and laboratory protocol, improves the quality of surveillance data. Previous criticisms of passive laboratory surveillance systems include the underreporting and lack of representativeness of disease. This study assesses substantive factors influencing laboratory reporting to passive surveillance systems. To our knowledge, this is the first study to investigate reporting consistency in the NREVSS surveillance.

Our study findings suggest that laboratories reporting directly to NREVSS are more consistent reporters than laboratories reporting via contractual agreement. This may be due to the absence of an intermediary between laboratory reporting and data accessibility in NREVSS. Another consideration may be increased awareness or knowledge among laboratories reporting directly to NREVSS surveillance. Antigen testing was the most common testing method used by laboratories and PCR testing has increased greatly over the years. This supports previous research suggesting antigen detection tests are currently the most common RSV test types used by US laboratories (Karma, M RS) and the increasing utilization of PCR testing over recent years. In the past, antigen detection was preferred RSV detection method to make an immediate diagnosis of RSV infection. Research has found PCR testing can be a more sensitive and timely confirmatory method than antigen detection (Liao, Tomalty, Majury, & Zoutman, 2009; Miernyk et al., 2011). Furthermore, the reduction in the turnaround time for PCR diagnostics and the

convenience of simultaneously identification of multiple viruses in one assay contributes to its growing favorability. Ultimately, multiple factors determine test selection including cost, laboratory protocols and requirements, laboratory setting, most appropriate patients, and duration of specimen availability. Based on these findings, we hypothesize PCR testing will continue to rise and possibly replace antigen reporting.

Regional location of laboratories also significantly contributed to reporting consistency. Laboratories located in the South and West region were found to be significant moderators in the consistency of reporting among direct and indirect reporters. Analysis of the subset reveals that this impact is specifically modified in antigen testing. Given the variation in RSV seasonality from region to region, this result may reflect the increased use of rapid antigen testing due to the extended seasonality of RSV in the southern region, especially in Florida (Bloom-Feshbach et al., 2013; Tang & Loh, 2014). Interestingly enough, the effect modification between reporter type and testing method and region was not seen in the subset of 50 laboratories. Given these laboratories are considered critical institution reporters for RSV, region and testing method did not influence reporting consistency.

Assessment of laboratory practices demonstrated that the majority of labs tested for RSV year round and had consistent laboratory practices on and off season. Testing year round was found to be a significant moderator in reporting consistency, while changes in testing protocol was not. This is plausible as the ability of laboratories to test year round allows for more RSV test reports while the protocol of testing may not necessarily impact reporting. Similar to results of all laboratories, the analysis of the assessed laboratories found region and testing methods as significant contributors to RSV reporting.

Laboratory-based surveillance systems necessitate resources, facilities, and training (Jamison et al., 2006). Based on results from this study, laboratory capabilities and practices play an important role in consistency of RSV reporting to NREVSS. Consistent reporting allows for the ability to effectively monitor trends in RSV that correspond with RSV activity, instead of laboratory activity.

Strengths and Limitations

This study has several limitations. Due to the retrospective and cross sectional nature of this study, analysis was limited to the variables that existed in the database or were obtained from assessment at the time of assessment. This sampling method may over represent pediatric and/or urban populations as well as laboratories that commit resources to reporting process and disease surveillance. Also, laboratory testing practices are not the only factor influencing how accurately the surveillance data reflects the epidemiological trends of RSV infections.

A strength of this study is its assessments to improve understanding of laboratories reporting to NREVSS. Laboratory variables were collected using a standardized questionnaire. Almost all of the exposure variables considered in this analysis were found to be significant predictors of reporting consistency, and these findings were reasonable and corresponded with previous findings on similar surveillance platforms.

Conclusion

Continued data collection and research is necessary to better understand and draw conclusions concerning the factors influencing RSV reporting to NREVSS surveillance. Further

exploration on year round laboratory testing practices of laboratories and diagnostics will provide a richer understanding and improve data quality. This study suggests direct reporting and testing methods are good measures of reporting consistency and allow for more representative data on RSV circulation.

Table 1a: Descriptive Characteristics of all laboratories reporting Respiratory Syncytual Virus to National Respiratory and Enteric Virus Surveillance System, July 2003-June 2013

		All Test Types			Antigen detection				Culture				PCR			
		Labs	Tests	Lab weeks	Labs	Lab weeks	p-value	Median weeks	Labs	Lab weeks	p-value	Median weeks	Labs	Lab weeks	p-value	Median weeks
Overall		884	4,989,768	188,994	884	139,197		40	240	34,841		44	160	14,956		41
Census Region	**Northeast**				151	22,461	<.0001	37	39	5,900	0.8917	45	32	2,752	0.3707	40
	Midwest				215	32,428		39	74	10,991		45	43	4,939		46
	South				342	56,667		42	76	10,832		44	47	3,624		39
	West				176	27,641		41	51	7,118		46	38	3,641		46
Reporter Type	**Direct**				90	27,685	<.0001	49	69	19,607	<.0001	51	47	5,819	0.0575	50
	Indirect				794	111,512		39	171	15,234		30	113	9,137		39
Contract season	**1 (2003-2006)**				93	10,476	<.0001	51	69	7,583	<.0001	51	6	119	<.0001	2
	2 (2006-2010)				825	74,879		38	199	16,203		41	83	4,061		32
	3 (2010-2013)				550	53,842		45	136	11,055		46	139	10,776		46

Table 1b: Descriptive Characteristics of subset of 50 assessed laboratories reporting Respiratory Syncytual Virus to National Respiratory and Enteric Virus Surveillance System, July 2003-June 2013

		All Test Types			Antigen detection				Culture				PCR			
		Labs	Tests	Lab weeks	Labs	Lab weeks	p-value	Median weeks	Labs	Lab weeks	p-value	Median weeks	Labs	Lab weeks	p-value	Median weeks
Overall		50	1,351,771	28,613	50	16,729		50	27	8,282		52	26	3,602		52
Census Region	**Northeast**				9	2,576	0.1797	51	3	1,162	0.0082	52	3	442	0.0258	52
	Midwest				11	3,846		51	8	2,712		52	7	1,051		52
	South				17	5,732		50	8	1,764		52	9	605		52
	West				13	4,575		52	8	2,644		52	7	1,504		52
Reporter Type	**Direct**				22	9,397	<.0001	52	16	6,371	0.0001	52	19	2,712	0.9953	52
	Indirect				28	7,332		46	11	1,911		49	7	890		52
Contract season	**1 (2003-2006)**				23	2,987	0.0741	52	18	2,281	0.1281	52	1	10	0.1501	10
	2 (2006-2010)				50	7,636		51	24	3,645		52	12	1,037		52
	3 (2010-2013)				48	6,106		51	22	2,356		52	26	2,555		52

Table 1c: Median Respiratory Syncytial Virus tests and weeks reported per test type and season for all laboratories reporting to National Respiratory Enteric Virus, July 2003-June 2013

							Antigen Detection		Cuture Detection		PCR	
		Labs	**RSV Tests**	**Median RSV Tests**	**Weeks**	**Median Weeks**	**Median RSV Tests**	**Median Weeks**	**Median RSV Tests**	**Median Weeks**	**Median RSV Tests**	**Median Weeks**
Season		n=884	4,989,768	338.00	188,994	38	291.00	38	519.00	43	962.00	38
2003-2004		87	171,748	811.50	5,741	47	880.50	47	718.50	49	—	—
2004-2005		92	208,858	927.00	6,179	49	927.00	47	989.00	51	9.00	1
2005-2006		89	231,810	1144.50	6,258	49	1160.00	48	1208.00	51	14.50	6
2006-2007		384	383,717	303.00	15,198	34	284.50	34	438.00	38	206.50	19
2007-2008		628	602,850	308.00	24,757	36	285.00	36	514.50	40	228.50	15
2008-2009		687	686,433	295.00	28,831	38	275.00	38	530.50	40	653.50	26
2009-2010		651	758,780	238.00	26,357	34	203.00	31	503.00	41	1236.00	39
2010-2011		535	651,031	325.00	24,452	38	276.00	37	351.00	40	1009.00	38
2011-2012		516	568,340	330.00	26,017	43	275.00	42	354.00	47	1041.00	44
2012-2013		501	726,201	367.00	25,204	43	324.00	42	429.00	45	1594.50	45

Table 2: Laboratory practices for Respiratory Syncytial Virus reporting to National Respiratory and Enteric Virus Surveillance System, July 2003-June 2013 (Subset of 50 Assessed Laboratories)						
	All Labs		Direct Laboratories		Indirect Laboratories		p-value
Census Regions	n=50	%	n=22	%	n=28	%	
NE	9	18.00%	4	18.18%	5	17.86%	0.6857
MW	11	22.00%	6	27.27%	5	17.86%	
S	17	34.00%	8	36.36%	9	32.14%	
W	13	26.00%	4	18.18%	9	32.14%	
Diagnostic Reporting	n=50	%	n=22	%	n=28	%	
Antigen	50	100.00%	22	100.00%	28	100.00%	
Culture	27	54.00%	16	72.73%	11	39.29%	
PCR	26	52.00%	19	86.36%	7	25.00%	
Selection of testing method	n=50	%	n=22	%	n=28	%	
Standard protocol	22	44.00%	9	40.91%	13	46.43%	0.0264
Physician order	20	40.00%	11	50.00%	9	32.14%	
Both	8	16.00%	2	9.09%	6	21.43%	
Test for RSV year round	n=50	%	n=22	%	n=28	%	
Yes	46	92.00%	19	86.36%	27	96.43%	0.3079
No	4	8.00%	3	13.64%	1	3.57%	
Lab practices change on and off	n=50	%	n=22	%	n=28	%	
Yes	14	28.00%	12	54.55%	2	7.14%	<.0001
No	36	72.00%	10	45.45%	26	92.86%	

Table 3. Model for the association between reporter type, census region, and consistent reporting for all laboratories reporting to National Respiratory and Enteric Virus Surveillance System, July 2003-June 2013

	Crude Model			Model stratified by all interaction terms*			Model with Interaction Terms					
							Antigen		Culture		PCR	
	Adjusted Odds Ratio	95% CI	p-value	Adjusted Odds Ratio	95% CI	p-value	Adjusted Odds Ratio	p-value	Adjusted Odds Ratio	p-value	Adjusted Odds Ratio	p-value
Exposure												
Indirect Reporters	Reference		<.0001	Reference		<.0001	Reference	<.0001	Reference	<.0001	Reference	0.2671
Direct Reporters	2.706	2.311-3.168		2.8	2.384-3.288		1.725		2.411		1.127	
Moderators												
Region			0.003									
Northeast	Reference						Reference	<.0001	Reference	0.0763	Reference	0.1971
Midwest	1.066	0.899-1.264					0.744		0.864		1.004	
South	1.294	1.102-1.52					1.277		0.766		0.82	
West	1.248	1.041-1.494					1.411		1.172		1.508	
Contract Season (Year)			<.0001									
2003-2006	Reference											
2006-2010	0.494	0.378-0.645										
2010-2013	0.803	0.61-1.057										
Testtype			0.0002									
Antigen	Reference											
Culture	0.881	0.756-1.026										
PCR	0.653	0.531-0.804										
Reporter Type*Region												
Direct*Northeast							Reference	0.0006	Reference	0.5144	Reference	0.0029
Direct*Midwest							0.746		1.14		0.948	
Direct*South							1.031		0.919		0.643	

*Stratified on interaction terms test type, region, and contract season

	Table 4. Model for the association between reporter type, census region, and consistent reporting for 50 assessed laboratories reporting to National Respiratory and Enteric Virus Surveillance System, July 2003-June 2013									
	Crude Model			Model stratified by all interaction terms*			Model with Interaction			
							Standard protocol		Physician order	
	Adjusted Odds Ratio	95% CI	p-value	Adjusted Odds Ratio	95% CI	p-value	Adjusted Odds Ratio	p-value	Adjusted Odds Ratio	p-value
Exposure										
Indirect Reporters	Reference		<.0001	Reference		<.0001	Reference	<.0001	Reference	0.0066
Direct Reporters	3.95	2.445-6.382		4.935	2.878-8.462		2.369		4.174	
Moderators										
Region			0.002					0.1517		0.2178
Northeast	Reference						Reference		Reference	
Midwest	1.124	0.609-2.075					0.67		1.93	
South	1.484	0.803-2.742					0.67		1.993	
West	3.015	1.554-5.851					2.03		4.976	
Testtype			0.0042			0.0049		0.6488		0.0058
Antigen	Reference			Reference			Reference		Reference	
Culture	1.061	0.665-1.692		1.11	0.695-1.774		0.993		1.821	
PCR	0.425	0.247-0.732		0.433	0.249-0.754		0.806		0.45	
Test RSV All year								0.3877		0.5907
No							Reference		Reference	
Yes							1.402		1.13	
Testing Protocol Change On-Off Season			0.0006			0.0005				
No	Reference			Reference						
Yes	0.434	0.269-0.699		0.392	0.232-0.662					
Selection of testing method			0.0285							
Standard protocol	Reference									
Physician order	0.669	0.432-1.035								
Both	0.46	0.250-0.850								
Interaction										
Reporter Type*Region								0.2111		0.0302
Direct*Northeast							Reference		Reference	
Direct*Midwest							0.855		0.159	
Direct*South							0.576		0.763	
Direct*West							0.935		-	
*Stratified on interaction terms test type, region, and contract season										

Table 5. Model for the association between reporter type, census region, and consistent reporting for laboratories reporting to National Respiratory and Enteric Virus Surveillance System, July 2003-June 2013

	All Labs						50 Labs					
	Model			Model with Interaction			Model			Model with Interaction		
		$R^2 = 0.0622$			$R^2 = 0.0578$			$R^2 = 0.0877$			$R^2 = 0.1588$	
Exposure	β	(se)	p	β	(se)	p	β	(se)	p	β	(se)	p
Reporter Type												
Indirect Reporters												
Direct Reporters	0.4977	0.0403	<.0001	0.5224	0.0469	<.0001	0.6869	0.1224	<.0001	0.2325	0.1505	0.1223
Covariates												
Region												
Northeast	Reference			Reference			Reference			Reference		
Midwest	-0.0718	0.0488	0.1406	-0.1698	0.0612	0.0055	-0.2871	0.1666	0.0848	-0.5148	0.1902	0.0068
South	0.1221	0.0443	0.0058	0.0578	0.0583	0.3213	-0.00894	0.1653	0.9568	-0.0774	0.1834	0.673
West	0.0854	0.0534	0.1096	0.2884	0.0783	0.0002	0.6999	0.1904	0.0002	0.7229	0.2724	0.008
Contract Season												
2003-2006	Reference											
2006-2010	-0.3974	0.0524	<.0001									
2010-2013	0.0892	0.0557	0.1093									
Testtype												
Antigen	Reference			Reference			Reference			Reference		
Culture	0.0576	0.0577	0.3185	0.161	0.0617	0.0091	0.3248	0.1586	0.0406	0.3469	0.1646	0.0351
PCR	-0.2418	0.071	0.0007	-0.3048	0.0721	<.0001	-0.5903	0.1788	0.001	-0.4827	0.1885	0.0105
Test For RSV all year												
No												
Yes										0.4867	0.1654	0.0033
Testing Protocol Change On-Off Season												
No							Reference					
Yes							-0.4176	0.1216	0.0006			
Selection of testing method												
Standard protocol							Reference			Reference		
Physician order							-0.00982	0.1475	0.9469	0.1341	0.1735	0.4394
Both							-0.3829	0.1944	0.0489	-0.5105	0.2372	0.0314
Interaction												
Reporter Type*Region												
Direct*Northeast				Reference						Reference		
Direct*Midwest				-0.1309	0.0612	0.0324				-0.4775	0.1899	0.0119
Direct*South				-0.1097	0.0583	0.0598				-0.3764	0.1833	0.04
Direct*West				0.2723	0.0783	0.0005				0.2891	0.2642	0.2737
Reporter Type*Test type												
Direct*Antigen				Reference								
Direct*Culture				0.3818	0.0617	<.0001						
Direct*PCR				-0.4186	0.0721	<.0001						
Selection of testing method												
Direct*Standard protocol										Reference		
Direct*Physician order										0.6618	0.167	<.0001
Direct*Both										-1.3166	0.2355	<.0001

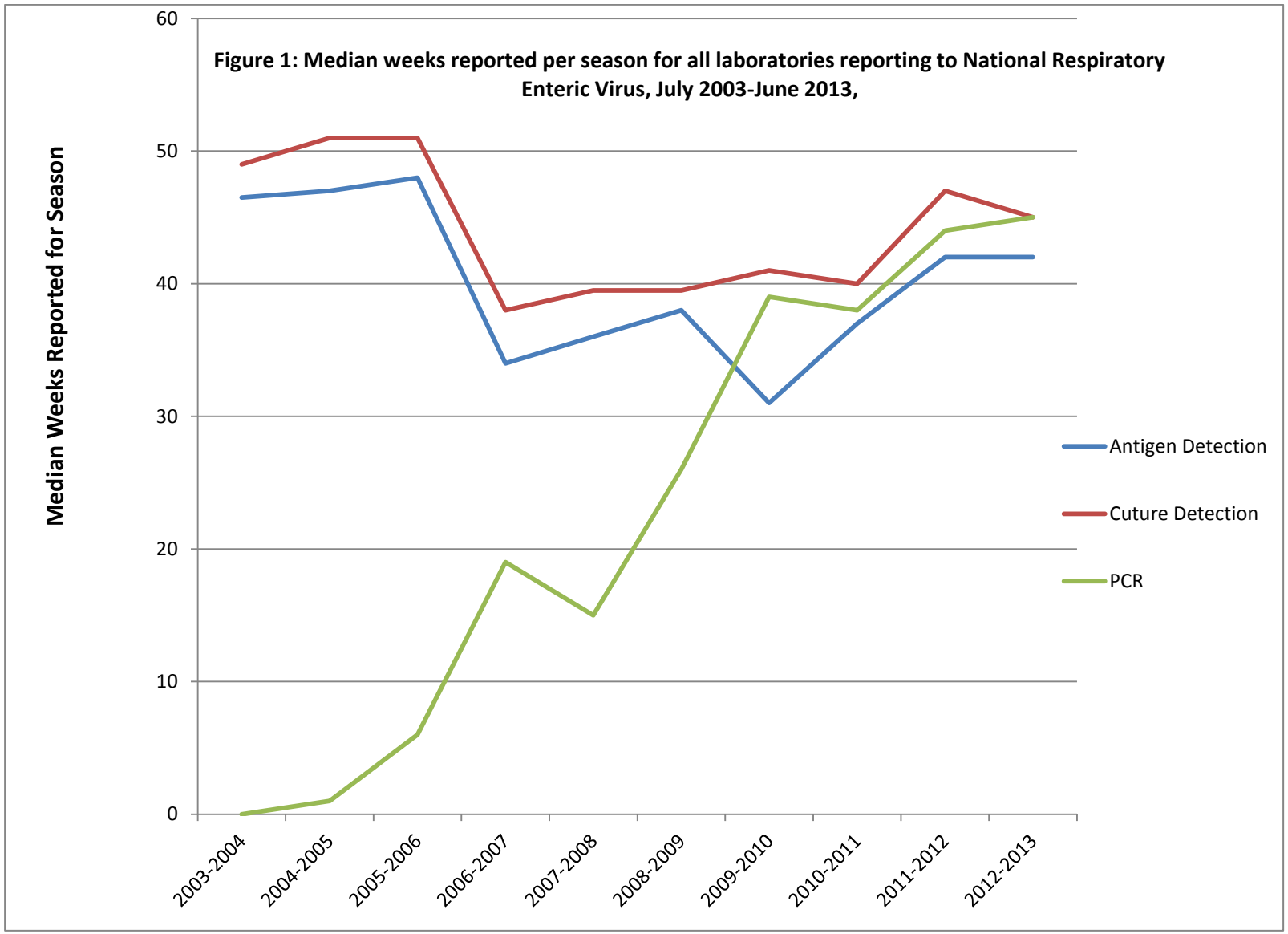
Figure 1: Median weeks reported per season for all laboratories reporting to National Respiratory Enteric Virus, July 2003-June 2013,
Median Weeks Reported for Season
60
50
40
30
20
10
0
2003-2004
2004-2005
2005-2006
2006-2007
2007-2008
2008-2009
2009-2010
2010-2011
2011-2012
2012-2013
Antigen Detection
Cuture Detection
PCR

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