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A Research Framework for Evaluation of RSV Vaccination Use and RSV Outcomes Among Premature Infants Under One Year of Age

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A Framework for Evaluation of RSV Vaccination Use and RSV Outcomes Among Premature
Infants Under One Year of Age

By

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ABSTRACT

Respiratory Syncytial Virus (RSV) infects the lower respiratory tract in children under the age of two years and is spread through droplet and contact with infected persons. An estimated 200,000 children suffer from complications of RSV annually worldwide. Palivizumab is a monoclonal antibody used to immunize children from RSV and has been on the market since 1988. In 2014, the American Academy of Pediatrics (AAP) updated its policy for recommendation of RSV in premature infants. The objective of this capstone is to propose an evaluation framework with an example of how it could have been applied to assess the impact of the AAP policy change on RSV vaccination use and RSV outcomes among premature infants.

The proposed evaluation framework would be a unique link between birth certificate records and surveys of parents/guardians of 32 week gestation premature infants or less in the metropolitan Atlanta area. The birth certificate data would identify “at risk” infants and would allow for selection of a sample of parents/guardians, both pre-policy change (August 1, 2013 to July 30, 2014) and post-policy change (August 1, 2014 to July 30, 2015). The primary endpoints would be: initiation and completion of the RSV vaccine series and RSV infection rates.

Moderating variables would be obtained from birth certificate data (e.g. mother’s education and race) and survey data (e.g. attitudes toward vaccine acceptance).

The evaluation framework proposed in this Capstone can be used in future analyses of RSV vaccination policy changes. It can also be generalized to other geographic areas in the US and used for routine surveillance of RSV vaccination use and RSV outcomes.

APPROVAL PAGE

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Author's Statement Page

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CHAPTER I: INTRODUCTION

Background

Respiratory Syncytial Virus (RSV) infects the lower respiratory tract in children under the age of two years and is spread through droplet and contact with infected persons. An estimated 200,000 children suffer from complications of RSV annually worldwide. Once RSV is acquired, an estimated 25% to 40% of children under the age of one year suffer from severe complications of the infection (RSV, 2015). It can be prevented with Palivizumab, a monoclonal antibody used to immunize children from RSV and has been on the market since 1988 (Mahadevia et al., 2012). In 2014, the American Academy of Pediatrics (AAP) updated its Palivizumab policy guidelines for recommendation of RSV in premature infants.

Some of the symptoms of RSV include cold like symptoms of runny nose, cough, and fever in healthy children (RSV, 2015). Immuno-compromised children suffer from more severe complications of lower airways such as bronchiolitis, croup, and pneumonia. The more severe cases of RSV places babies at risk for hospitalization, oxygen therapy, airway clearance, intubation and Extra Corporeal Membrane Oxygenation (ECMO), also known as lung bypass (Regnier et al., 2013).

Due to less developed lung tissue, premature infants are at risk of having severe complications from RSV. Fetal lung development begins around 22-25 days after conception. Although there are 5 stages of lung development, the last two stages, saccular from 24-38 weeks gestation and alveolar from 36 weeks gestation up to 3 years of age, places infants at risk for surfactant deficiency, chronic lung disease, and bronchiolitis (Rubarth and Quinn, 2015). Table 1 displays the stages of lung development in the growing fetus and infants. Many studies

show that infections of the lower airway during any of these lung development stages can have long term effects of asthma, wheezing, and chronic lung disease (Hall et al., 2013).

Table1. Stages of Lung Development in Fetus and Infant

Stage of Development	Fetal Time Period	Events Occurring	Possible Defects
Embryonic	3-7 weeks	Respiratory bud forms, trachea and larynx forms	TEF, pulmonary agenesis
Pseudo-glandular	6-16 weeks	Branching continues, terminal bronchioles	CDH, tracheal atresia, pulmonary hypoplasia
Canalicular	16-28 weeks	Development of bronchioles, vascularized lung tissue, gas exchange at 24 weeks	RDS
Saccular	24-38 weeks	Terminal sac increase, surfactant production	RDS
Alveolar	36- 3 years	True alveoli develop	BPD

Helfrich et al. 2015

Abbreviations: TEF, tracheoesophageal fistula; CDH, congenital diaphragmatic hernia; RDS, respiratory distress syndrome; BPD, bronchopulmonary dysplasia.

Premature infants are more susceptible to severe symptoms of RSV due to their less developed lung volumes and alveoli, inability to fight off infection, and feeding issues. Infants born at less than 35 weeks gestation are particularly at higher risk for jaundice, chronic lung disease, respiratory distress, and longer hospital stay compared to term infants of 37 to 40 week gestation (Helfrich et al., 2015). Nonetheless, many studies have been performed on the mid and late preterm infants ranging from 30 to 36 weeks gestation concerning effectiveness of Palivizumab and hospitalization of infants with RSV (Helfrich et al., 2015). Figure 1, shows the difference in lung volume and alveoli in preterm and a well vascularized term infants lungs.

Figure 1. Preterm infant Lungs Versus Term Infant Lungs



(Moore and Persaud, 2008; Synagis, 2015)

Objective

The objective of this capstone project is to develop a framework to evaluate the RSV vaccine initiation, RSV vaccine completion, and acquired RSV infection in premature infants.

Specific aims of this Capstone are:

- 1) Propose an evaluation framework that would involve a unique link between birth certificate records and a survey of parents/guardians with premature infants identified through the birth certificate records

- 2) Provide an example of how the evaluation framework could have been used to assess the impact of a policy change regarding Palivizumab vaccination by the American Academy of Pediatrics in 2014.
- 3) Provide an example of how the evaluation framework can be used for annual surveillance of RSV vaccination use and RSV outcomes in premature infants

CHAPTER II: LITERATURE REVIEW

Cost Effectiveness of RSV Vaccination

According to the CDC, in 2014 nearly 58,000 children under the age of five years were diagnosed, hospitalized, and treated for complications from RSV (RSV, 2015). The cost burden for RSV infection ranges anywhere from 17,000 to 60,000 dollars per hospitalization per child (Regnier et al., 2013). Palivizumab immunization was found to be cost effective in early, mid, and late premature infants who were given the vaccination at or under the age of 6 months with more than one risk factor (Mahadevia et. al., 2012). Some of the risk factors for low vaccination status are parental vaccine acceptance, lack of healthcare access, and burden of monthly injections during the RSV season. The Mahadevia et al. (2012) study examined three groups of premature infants without lung disease or congenital heart defects. This study found the RSV vaccination to be cost effective in premature infants with more than one risk factor. It is strongly recommended by AAP that children with lung disease, congenital Heart disease, and diseases of airway clearance also receive the vaccination to avoid lengthy hospital stays (Committee on Infectious Disease, 2014).

A study by S. Riegner (2013) analyzed the healthcare utilization costs for RSV and Palivizumab vaccine efficacy. This study observed RSV infection and the incidence of asthma and other sequelae following an RSV infection in children. According to the author, asthma and wheezing related to RSV decreases as age increases (Riegner, 2013). This study also accounts for loss from work, transportation to and from hospital, sequelae costs, funeral costs and lost income from premature death (Regnier, 2013). According to this study, RSV vaccination could prevent 23,069 hospitalizations and 66 deaths of infants in the USA. Although, less than 3% of

total RSV infected children require hospitalization from severe symptoms, the majority of hospitalizations for RSV are 6 months and younger (Kenyunju et al., 2015). 69% of infants are infected their first year of life (Regnier et al., 2013.) Nearly all children are infected by two years of age (RSV, 2015).

Although only 3% of RSV infections require hospitalization, the estimated cost of RSV burden on United States economy is higher for preterm infants than term infants. The average cost for a preterm infant is \$34,000 per RSV hospitalization versus \$9,000 for term infants (Shi et al., 2011). The cost for a series of 5 Palivizumab injections over an RSV season can range anywhere from 10,000 to 15,000 (Gutfraind et al., 2015). The study results vary from state to state, however hospitalization rates of 30 to 50 per 1000 in infants less than 6 months old was the average. This was the highest number of hospitalizations among each of the groups studied. The other two groups of infants were 6 to 12 months and greater than 12 months with hospitalizations at 11 to 15 per 1000 infants and 15 to 26 per 1000 infants respectfully (Hall et al, 2013). Variability in hospitalization rates among early-preterm, late-preterm, and term infants are limited by small sample size in this particular study, but many other studies have explored Intensive Care Unit admissions and severity of symptoms in RSV positive children with less variability.

A small percentage of children acquire RSV despite vaccination. One retrospective study by Butt et al. (2009) examined the characteristics of 181 patients admitted to a Pediatric Intensive Care Unit (PICU) with RSV infection following the implementation of RSV prophylaxis. Approximately 3% of children who received Palivizumab were diagnosed with RSV. The other 97% of children vaccinated did not acquire RSV. According to this study, four infants were

preterm (range 27–32 weeks gestational age), whereas two resulted in death; 66.7% had one or more underlying medical condition, such as congenital heart disease, chronic lung disease, a neurological disorder or a genetic syndrome (Butt et. al, 2011). 50% of the premature infants admitted to PICU in this study resulted in death.

A study by Borse et al. (2014) was performed on Alaska Native Infants. Alaska Native infants have high rates of RSV and are hospitalized more often from complications associated with RSV. Alaska Native infants have 5 times the rate of hospitalization than the national average and an RSV season almost twice as long as some states. The cost per vial of Palivizumab is around \$1000 per 0.5 mL vial. The dose is weight dependent at 15mg/kg. The average term baby weighs around 3.5 kg which would be 0.53mL or an estimated \$1000 per child per injection. Although the premature infant can weigh significantly less than a term infant, the cost for premature infants to receive anywhere between 5 and 7 injections can be \$5000-\$7000 per premature child per RSV season (Synagis, 2016). However, the cost of hospitalization in Alaska is \$3387 per day with an average length of hospital stay for a preterm infant is 7.1 days; an infant can easily generate a \$42000 bill (Borse et al., 2014).

Factors Affecting RSV Rates

There are several factors that increase the risk of acquiring RSV infection. Other than immunization, the best way to prevent RSV infection is to reduce exposure. RSV is significantly reduced in infants kept away from daycare, children who are homeschooled, who have no siblings, good handwashing, and babies born to non-smoker families (Heikkinen et. al., 2015). Day care attendance can affect whether a child acquires this highly contagious virus by

increasing contact with other sick children. Unfortunately, many households require both parents to work and homeschooling or keeping the infants away from outside childcare is not an option. Also, infants with siblings that attend school or day care could increase exposure to RSV (Abraha et al., 2015).

The second factor that increases an infant's risk of acquiring RSV infection is the number of siblings and family members in the household. Many infants acquire RSV from a sibling or someone positive in the home during the winter months. Vaccination of family members may be a productive way of keeping the infant from acquiring this infection (Kanyunjui et al., 2015). Another study evaluated the number of siblings and sibling ages with infants who were hospitalized. In children under the age of two years old who were hospitalized with RSV complications, 76% resided in homes with at least one other sibling (Hall et al., 2013). A prospective study found that 77% of the RSV cases had family members with positive nasal swabs (Heikkinen et al., 2015). Nasal swabs are a simple non-invasive way to detect the RSV viral antigen in the nares and is the main method used by physicians and health care facilities to diagnose RSV (Kanyunjui et al., 2015; Abraha et al., 2015). Heikkinen et al. (2015) suggest that immunization of family members could possibly decrease the incidence of premature infants acquiring RSV.

Children in households with family members who smoke are at greater risk of having severe complications and hospitalization from RSV than children who are not exposed to second hand smoke (Heikkinen et al., 2015). Smoking among family members not only increases respiratory illness in adults, it affects children in the home, but at a much higher rate than adults (Smoking and Tobacco use, 2015). Children exposed to second hand smoke acquire

asthma, bronchitis, and pneumonia more frequently than children who are not exposed due to the potential decrease of the lower lung development from the chemicals in smoke (Smoking and Tobacco Use, 2015).

The age at which a premature infant is exposed can affect RSV rates, severity, and hospitalization. Unfortunately infants under the age of six months appear to have the most severe cases of RSV infection, while older children and other family members are often carriers of RSV (Heikkinen et. al., 2015; Abraha et. al., 2015). The results of one other study found that hospitalization rates of 30 to 50 per 1000 infants for babies less than 6 months old is double that of infants greater than 12 months old (Hall et al., 2013). The study by Kenyunjui et al. examined RSV herd immunity and, again, suggested that vaccinating older siblings could help prevent RSV in babies under the age of 6 months. They found that a reduction in hospitalization could range from 50-70% by vaccinating older children (Kenyunjui et. al., 2015).

Factors Affecting Parents' Vaccine Acceptance

RSV vaccination and vaccine acceptance rates are difficult to estimate. For one, since it is not a mandatory vaccination, it does not require reporting to the CDC (Vaccine Coverage, 2015). Secondly, many infants do not receive the total number of recommended Palivizumab injections during the RSV season. In 2012, Chadha et al. (2012) explored adherence to recommendations for Palivizumab dosing and found that it is suboptimal in preterm infants insured by the South Carolina Medicaid program. Only 36%-46% actually received the total recommended doses. This study did not take into account data from private insurance companies in the area for comparison. In conclusion, they suggested healthcare professionals play a vital role in identifying and following up with patients who qualify for Palivizumab dosing

in populations with lower SES. Despite the solid evidence of the benefits of Palivizumab in high-risk groups, many who are eligible are not obtaining the vaccination as recommended in the South Carolina Medicaid Program (Chadha et. al. 2012: Hall et. al., 2012).

There are several factors that affect vaccine acceptance or opposition among parents. Many parents want to know the risks versus the benefits. A health care provider can provide literature to determine risks versus benefits. Physician and medical staff play a role as educators to patients and family members concerning RSV vaccination and prematurity. Vaccine education may include information on side effects, safety, and efficacy. One study, by Zimet (2005) explored how parents relied heavily on whether their physician felt the HPV vaccine safe and necessary. Several registries, such as Vaccine Adverse Event Reporting System (VAERS), were developed to report adverse reactions from vaccines and medical equipment so that parents and health care providers could have accurate and update information (VAERS, 2016). Approximately 25% of parents in one study fear that vaccines will lower the child's immune system or cause autism or multiple sclerosis (Gaskey et al., 2009).

Following vaccine injection, 10% of patients have a rash or fever up to 3 days (Synagis, 2016). The Canadian Registry of Children Receiving Palivizumab (CARESS) was developed specifically for reporting adverse reactions to RSV vaccination in Canada. To date, only one case of anaphylaxis following the Palivizumab injection in an infant has been documented and published as a case study (Savitz et al., 2014). This study found that out of 13,025 infants that received the Palivizumab injections, 14 hypersensitivity reactions were reported related as possibly or probably due to RSV vaccine in six infants. That's 2.8 per 10,000 or .05% of infants

having serious complications from RSV vaccinations (Jinghan et al., 2015). This number is, however, considered safer than the influenza vaccine as reported by the U.S. VAERS. The influenza vaccine had a risk of febrile seizures reported as 1 per 1,000 children or 0.1% with this complication in high risk infants (VAERS, 2016).

Several studies have been published on parental vaccine acceptance and Human Papilloma Virus (HPV) vaccines. The HPV vaccine is similar to RSV in that 1) the patient receives multiple doses over a six month time period and 2) the vaccines are not mandatory for school or day care attendance. There could be increased completion of vaccines with a reminder protocol in place and school-based vaccine programs (Neubrand et al., 2009). A study by Gerend et al. (2009) observed vaccine attitude responses of parents of daughters who fit the criteria for HPV vaccine. Greater than 60% had intentions to vaccinate, with 50% actually receiving the HPV vaccine series (Gerend et al., 2009). Reminders to parents and guardians of infants and children can improve the rates of vaccine completion (Neubrand et al., 2009).

How physicians respond to patients concerns, patient physician trust, and the number of patient visits can all affect completion of a vaccine series. Although many parents are not aware of some of the consequences of some infections, many parents are very interested in efficacy and physician recommendations. In one article, it was suggested that a goal for physicians should be to acknowledge and have a positive conversation with parents concerns about vaccination (Zimet, 2005).

CHAPTER III: METHODS

Example 1: AAP Policy Change

This example illustrates a hypothetical evaluation of infants of 29 weeks gestation or less and infants 29-32 weeks gestation for initiation and completion of RSV vaccine series and for acquired RSV infection pre- and post- policy guideline changes proposed by the American Academy of Pediatrics (AAP). The AAP policy guideline change is summarized in Table 2.

Table 2. Summary AAP policy guideline changes published August 1, 2014

	Pre-policy guidelines	Post-policy guidelines
Gestational age recommended at less than one year of age at start of RSV season	32 week gestation	Less than 29 week gestation
Number of recommended injections at start of RSV season	6 injections	5 injections
At risk groups	Premature, heart disease(may have up to 2 years of age), Chronic Lung disease, airway clearance diseases	Premature, heart disease, Chronic Lung disease, airway clearance diseases

Study Design

The American Academy of Pediatrics (AAP) is an organization that dedicates its work to infants and children through evidence-based practice. In 1988, the AAP developed a policy guideline for practitioners on the administration of Palivizumab following the Food and Drug Administration (FDA) approval and has been revised and updated in 2009, 2012, and 2014 (Committee on Infectious Disease, 2014). The original policy guideline of 1988 recommended the population at risk of severe complications which includes infants one year or less at the

start of RSV season who are less than 35 weeks gestation, infants with chronic lung disease, congenital heart defects, and disorders that decrease lung clearance, such as cystic fibrosis receive Palivizumab (Committee on Infectious Disease, 1988). In the policy update of RSV guidance for Palivizumab prophylaxis, developed and printed in 2014, the gestational age at which a premature infant was recommended to receive the vaccine was changed from less than 32 weeks gestation to less than 29 weeks gestation. Premature infants between the ages of 29 and 32 weeks gestation are no longer recommended to receive the vaccine.

This capstone project proposes a framework to evaluate responses to RSV vaccine recommendations for premature infants in the AAP policy guideline update. Birth certificate data will be used to define the study sample from 28 counties in the metropolitan Atlanta area (28 County MSA Map, 2016). A parent RSV survey questionnaire will be used to assess RSV vaccination initiation and completion in less than 29 week gestational age infants and for infants of gestational ages 29-32 weeks, acquired infection in pre- and post- policy guideline changes.

Study Period

The policy guideline update was published August 1, of 2014. This project defines the pre-policy time period from August 1, 2013 to July 30, 2014. The post-policy time period will be defined as August 1, 2014 to July 30, 2015. This gives a total of two years, one year before and one year after the policy to evaluate the change.

Study Data

Birth Certificate Records

This project proposal uses birth certificate information to obtain a sample of premature infants from 28 counties in the metropolitan Atlanta area. I will obtain birth certificates from the Georgia Department of Vital Statistics (GDVS) for the time period of August 1, 2013 to July 30, 2015, based on a year prior to and a year after policy change on August 1, 2014 (Georgia Department of Public Health, Vital Records, 2016). The GDVS will require a request and acceptance of terms and conditions prior to use of private birth certificate information. The Georgia Birth Certificate in Appendix A has mother/guardian address and phone number at time of birth, gestational age, and county of birth. Gestational age will be used to determine those infants less than one year at the start of RSV season. The mothers/ guardian's address and phone number will be used as contact information for delivery of survey packets and postcard reminders. The Georgia Birth Certificate also includes type of insurance, prenatal care, occupation, age, education level, and race.

Multi-modal Survey

A written parent RSV survey tool will be developed and administered to a sample of mothers with infants of 32 weeks gestational age or less during the study period. With the decline of home phone landlines, written mail-back surveys are still one of the most reliable methods of administering survey with good response rates at approximately 50-70% (Rookey et al., 2012). A draft of the parent/guardian RSV survey instrument is included in Appendix B. With the use of Optical Character Recognition (OCR), data entry can be made simple. It converts

images typed, handwritten or printed into machine encoded text via scanner (Biondich et al., 2002).

Some of the proposed survey items were based on routine influenza immunization survey questions from the National Immunization Survey (Vaccine Coverage NIS, 2016). NIS includes information on attitudes toward immunization from influenza, Human Papilloma Virus (HPV) vaccinations, routine child immunizations and other information related to mandatory children vaccinations of Diphtheria, Pertussis, Tetanus (DPT) and Measles, Mumps, Rubella (MMR). An analogy between influenza vaccine and RSV vaccine was derived since there was little data to support RSV factors alone (Trivalent Influenza Vaccine Data, 2016).

Sample Size Estimate

I will administer the survey to a sample of mothers with infants of 32 week gestational age or less in the pre- and post-policy guideline change period. The target sample of completed surveys is 100 Caucasian and 100 African American mothers in the pre-policy sample period and 100 Caucasian and 100 African Americans in the post-policy sample period.

The total number of premature births in the metropolitan Atlanta should be sufficient to achieve an adequate sample size assuming there is a 50% response rate to the survey. In Georgia there were 128,748 births in 2014 (Vital Records, 2016: OASIS, 2016). Of these, approximately 59,731 (46.4%) were born to Black or white women in the metropolitan Atlanta area. Of these 34,021 were Caucasian mothers and 25,710 to African American mothers (OASIS, 2016). African American women have a higher premature birth rate than Caucasian

women. From national statistics, approximately 1.5% of births are between 29 and 32 weeks gestational age, giving us 510 Caucasian women and 386 African American women to sample (NVSS, 2014). Infants under 29 weeks gestation are roughly 0.92% of total births. However, survival rates are proportional to the gestational age. An infant born at 28 weeks gestational age has a higher chance of survival than a 25 week gestational age premature infant. My initial sample could be as high as 255 Caucasian and 118 African American responses from the survey during the post-policy guideline change. While this is not an exact range for RSV risk, I expect the approximate sample on this order of magnitude. For the pre-policy sample size estimate, I will use 2013 birth data.

Survey Administration

The survey will randomly sample Caucasian (N=100) and African American (N=100) mothers of premature infants of 29-32 gestational ages in the pre- and post-policy periods. A minimum of 50-60 completed surveys will be from Caucasian and African American women each in the pre- and post- policy period is desired. The approach will be used for infants less than 29 weeks gestational age.

The survey will be administered following the RSV season in Georgia using a mixed-mode (written mail-in form and online survey form) after March 30th. The initial mailing for each RSV season will be delivered to the address of the mother on the birth certificate beginning April 20. For the babies identified as pre-policy (between August 1, 2013 and February 28, 2014) candidates, mailings would be delivered April 20, 2014, had the framework been in effect prior to the AAP policy change. March marks the end of the season and eligible

infants will receive the vaccine at the next RSV season. Mothers of infants born March 1, 2014 through February 28, 2015 will receive a survey packet starting April 20, 2015. Mothers of infants born March 1, 2015 through July 30, 2015 would receive survey packets after the 2015-2016 RSV season beginning April 20, 2016. The timing of survey administration is designed to reduce recall bias by delivering the surveys to mothers as close to the RSV season as possible.

Packets will be delivered staggered every three weeks until all surveys have been disbursed. The mailing will include a cover letter with the website link to the online questionnaire, instructions, the survey instrument and a prepaid return envelope. Undeliverable returns will be investigated and an attempt to identify the current location of the mother via phone number. For unreturned surveys, a postcard reminder will be mailed after 2 weeks. The mothers that are contacted by phone will be mailed a new packet to the corrected address. A third mailing will be the entire packet to those addresses of unreturned surveys. The online survey format will be parallel to the written survey format. The online survey tool will have questions worded for online administration with a bubble answer method from reputable and confidential survey software company (Dillman et al. 2012). Data from the written survey will be entered by a trained research assistant into an Excel database. For the online portion, the birth certificate number will be the survey ID and the participant can create a login password. The online data will be linked to birth certificate through the birth certificate number.

Human Subjects

Birth certificates are not public records. The GDVS provides access to birth certificate record information for research purposes through a request process. I will gain access by requesting permission from the GDVS and following the application process and guidelines. I will also obtain IRB approval through the Office for Human Research Protections for Human and Children Subjects as necessary. IRB approval can either be obtained via online application or paper submission (IRB, 2015). Georgia State University has a process for registering and applying online through a program called iRIS. Appendix C shows IRB questions and potential responses. Most institutions require legal and compliance review to satisfy human subject related research.

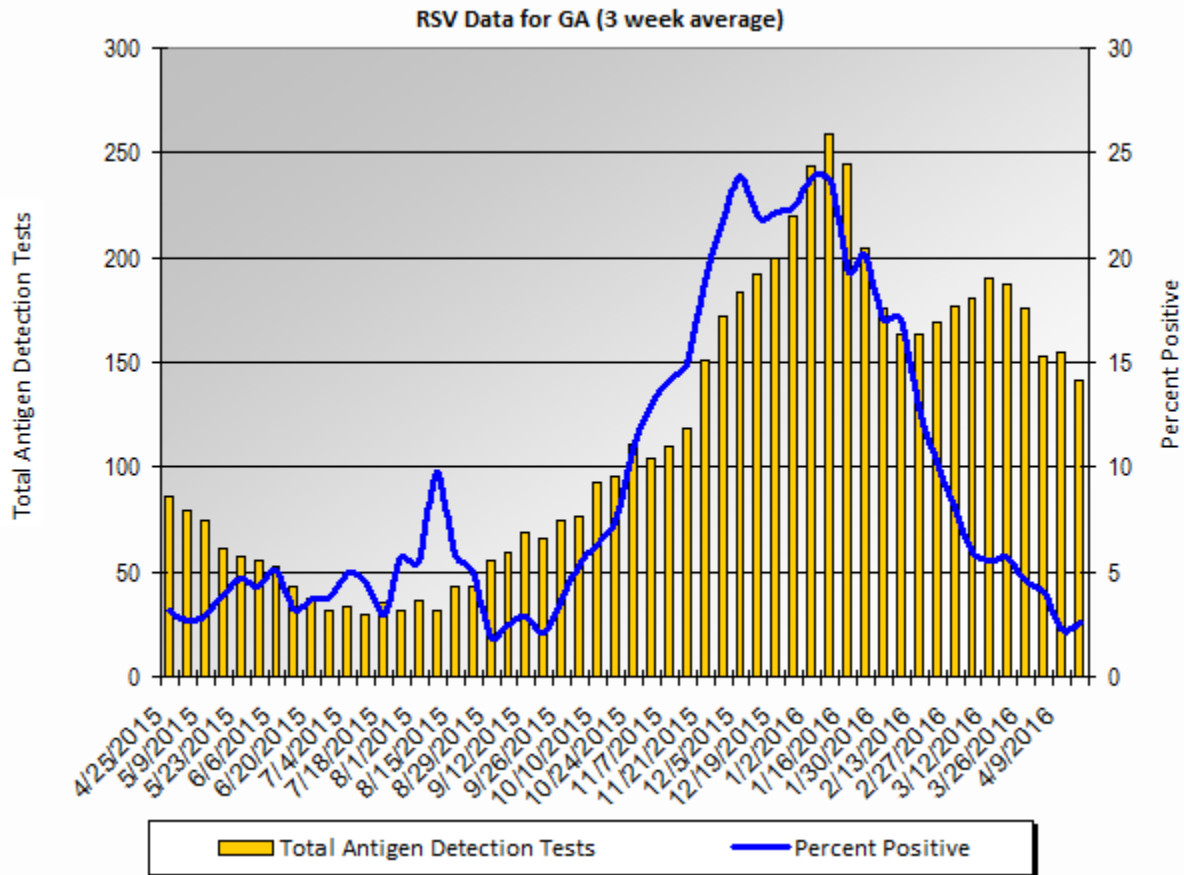
Example 2: Ongoing Surveillance of the RSV Season

In addition to providing (a hypothetical) assessment of how the AAP policy change might have affected RSV vaccination initiation and completion and RSV infection rates, the linked survey and birth certificate records could provide a framework for routine monitoring annually following the RSV season.

This proposed surveillance could complement current RSV surveillance. Current RSV surveillance monitoring is available from The National Respiratory and Enteric Virus Survey System (NREVSS) which shows RSV trends through positive RSV Antigen Detection Tests. Results are sent by state laboratories to NREVSS. These data are limited to state and national onset, peak, and ending of RSV season. These data can provide a context for comparison to the proposed survey timed measures of RSV infection rates in a particular state. Figure 2 shows a

NREVSS graph of total RSV Antigen Detection Tests with the percent positive test results. The RSV season is defined as a sharp slope in positive RSV antigen tests. In the state of Georgia, the RSV season is defined in the chart from October 1, to March 30 (NREVSS, 2015).

Figure 2. NREVSS data for Georgia



(NREVSS, CDC, 2016)

Study Measures

The study measures consist of primary endpoints which are noted in Table 3 as dependent variables. Table 3 also lists independent and other potential variables of interest that were gathered from the Georgia Birth Certificate and the parent RSV Survey. The

endpoints can be measured from survey data and analyzed with some of the various independent variables gathered from both the survey and the birth certificate.

Table 3. Variables for RSV Surveillance

Dependent Variables	Independent survey Variables	Potential Independent Variables
Vaccine initiated	Race	Maternal Age
Vaccine completed	Household size/siblings	Literacy
Acquired RSV	Use of Childcare	Marital Status
	Vaccine acceptance	Insurance Status

Table 2 lists the independent, dependent, and potential variables found on the survey questionnaire and the birth certificates.

Dependent Variables

The primary endpoints will be obtained from survey data. The three primary endpoints will be defined as:

Initiation: The premature infant received at least 1 RSV injection for the RSV season

Completion: The premature infant received at least 5 RSV injections for the RSV season

Infection: The premature infant had a positive RSV Antigen Detection Test or was told by a healthcare provider that the infant has RSV.

Independent Variables

The independent variables are: 1) mother’s race, 2) household size, 3) use of childcare, 4) vaccine acceptance, 5) maternal age, 6) literacy, 7) Insurance status, and 8) marital status. Mother’s race, age, marital status and insurance status are available from birth certificate records. Parental vaccine acceptance, household size and number of siblings, daycare attendance, literacy, and the primary endpoints are items on the RSV survey.

Insurance Status

Insurance status is a Georgia Birth certificate item. Insurance status will be classified as private, Medicaid, or uninsured. Studies indicate lower levels of health care and preventive services use in Medicaid plans. For example, Hall et al. (2013) as well as DeJongh et al. (2012) have compared private and Medicaid insurance on hospitalization and cost effectiveness in premature infants. Also, research performed in states with special circumstances, such as Alaska, use Medicaid data alone since all premature infants are Medicaid eligible (Borse et al., 2014).

Vaccine Acceptance

Vaccination acceptance is another unique variable of interest on the survey questionnaire. Parental attitudes vary from mandatory to non-mandatory vaccines. Mandatory vaccines such as Measles, Mumps, Rubella (MMR), Influenza, or Diphtheria, Pertussis, Tetanus (DPT) have nearly 100% vaccination rates in the state of Georgia (Trivalent Influenza Vaccine data, 2016 :NIS, 2015). RSV immunizations average 35-45% completion with many Primary Care Providers in some studies.

Maternal Age

Maternal age is located on birth certificate data and will be categorized into three groups. The largest group of mothers delivers infants between 20 and 34 years of age. Mothers under the age of 20 years are considered a teenage mother. Mothers greater than or equal to 35 years of age are considered advanced maternal age (Data and Statistics, 2016). Young

maternal age as well as advanced maternal age have been well studied for pregnancy outcomes and are at higher risk of having premature infants (Locke et al., 2012).

Number of Siblings

Siblings and other adults in the household can be carriers. An infant's risk of acquiring RSV increases with the number of siblings in the household that attend public or private daycares or schools (Kanyunjui et al., 2015). Palivizumab is not mandatory for daycare or school as with some other vaccines. The larger the household, the more potential exposure and risk of RSV for premature infants exist. Household size and number of siblings are question items on the survey.

Public Daycare

The use of public daycare can increase the risk of acquiring RSV in premature infants. Many infants can become exposed to RSV and many other viruses in environments with other infants and children (Abraha et al., 2015). A child is most contagious at 3-4 days once infected with RSV and begins displaying cold like symptoms. The child could remain contagious for a week or even longer in immune compromised children (RSV, 2015). It only takes one sick child to infect every other child in close proximity.

Mother's Education

Mother's education is available on birth certificate records and will be classified as: high school education (or GED) or less, some college or trade school, bachelor's degree from college or trade school, or post-graduate degree.

Mother's Literacy

The Single Item Literacy Screen (SILS) is a single question that is used to determine adult literacy and will be one of the survey items. This question determines how difficult it is to read printed health material and is rated 1-5 with 1= never and 5=always. The SILS question reads: "How often do you need to have someone help you when you read instructions, pamphlets, or other written material from your doctor or pharmacy?" (Morris et al., 2006). Most printed health material is on a marginal reading level of sixth-eighth (Badarudeen and Sabharwal, 2010). The SILS distinguishes functional reading level of less than 5th grade to marginal reading level. Based on this SILS, a score greater than two may indicate some level of difficulty with reading printed health related material used on the survey (Morris et al., 2006).

CHAPTER IV: STATISTICAL METHODS

Example 1: AAP Policy Change

Analysis of the AAP policy change will compare RSV vaccination initiation and completion and RSV infection rates between the pre- and post-policy RSV seasons (Appendix D). Two subsets of premature infants will be compared: those under 29 weeks of age, and those 29-32 weeks of age. This is important because post-policy the 29-32 week group was not recommended for RSV vaccination and a decrease in RSV vaccination rates might be associated with an increase in RSV infections.

Relationships between each of the endpoints and pre- and post-policy change periods will be evaluated by chi-squared statistics. I will use SAS 9.4 (SAS institute, Cary, NC) to test for significance using the conventional p-value of ≤ 0.05 . An example of the hypothesis to be tested is:

Null Hypothesis:

- No difference in RSV vaccine initiation among infants less than 29 weeks gestational age between the pre- and post-policy periods.

Alternative Hypothesis:

- Premature infants less than of 29 weeks gestational age will have a higher rate of RSV vaccine initiation in the post-policy period compared to the pre-policy period.

Example 2: On-going Surveillance of the RSV Season

Ongoing surveillance would follow the same general approach as described for Example

1. For example, the association of insurance status with each of the 3 endpoints could be annually evaluated among premature infants less than 29 weeks gestation:

Null hypothesis 1:

- There is no difference in RSV vaccination completion by insurance status.

Alternative hypothesis 1:

- There is a significant difference in RSV vaccination completion if the infant has private insurance or Medicaid.

Other examples with relevance for health policy or medical practice management are presented in Appendix E.

CHAPTER V: DISCUSSION

This capstone proposes a unique framework by using birth certificate records and a Parent RSV survey tool to evaluate RSV outcomes in premature infants. In my first example, I used the Palivizumab Update in policy guidelines by the AAP. No identifiable national databases such as NHANES could have been used to evaluate this policy guideline change in 2014 so I developed the proposed evaluation framework. Consequently, the impact of the AAP policy change remains unknown. It may be possible, however, to assemble other data to assess the impact. But, if my proposed evaluation framework (or something similar) had been in routine use in one or more locations in the US, then evaluation of the AAP policy change impact would have been possible.

The second example illustrates how my proposed evaluation framework can be used for ongoing surveillance framework of RSV vaccination status, RSV infection rates, and other factors that might affect these outcomes among premature infants. The linking of birth certificate records with survey results from a sample of parents/guardians of premature infants makes my capstone proposal innovative. Most other studies on RSV have used hospital and clinic data for routine surveillance. My proposed evaluation framework can be generalized for routine annual surveillance and to other locations in the US.

Limitations

One of the challenges with my proposed evaluation framework capstone is the number of premature infants could be potentially small due to low premature survival rates after birth. Many infants may not live to go home, particularly under 29 week gestational age. Most other

studies have very small numbers (less than 2.5% of infants born are less than 32 weeks gestational age) that show inconsistency and variability in outcomes due to sample size. Using this framework on an annual basis would allow the sample size to be increased through each additional year. This would allow for more reliable assessments of the associations such as maternal literacy or use of child daycare with RSV vaccine initiation and completion and RSV infection rates. There is also the potential for recall bias or for social desirability bias from mothers of premature infants who respond to the survey.

Summary

The RSV vaccine has been demonstrated to be safe and effective in preventing RSV infections among infants of 32 weeks gestational age and younger. I proposed an evaluation framework that uses birth certificate records to identify mothers of these premature infants, samples those mothers for survey, and links the survey responses to the birth certificate records. This framework could have been use to evaluate the AAP policy change on which “at risk” premature infants should have been vaccinated. One outcome of particular interest is the 29 to 32 week gestational age infant that might have been potentially affected by this policy change. This group of premature infants is no longer recommended to receive the Palivizumab vaccination. I also described how this approach of using birth certificate and survey data might be used for routine surveillance of RSV vaccine initiation and completion and RSV infection. Data collected from the birth certificate records and parent/guardian survey could also be helpful in understanding factors that affect RSV vaccine uptake and RSV infection rates.

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APPENDIX A

State of Georgia birth Certificate example

**State of Georgia
Birth Worksheet**

State File Number: _____

CHILD	First _____ Middle _____ Last _____		Suffix _____		
	Date of Birth: <u> </u> / <u> </u> / <u> </u> (MM/DD/YYYY)	Time of Birth: <u> </u> : <u> </u> : <u> </u> AM/PM	Sex: <input type="checkbox"/> Male <input type="checkbox"/> Female	Name of Facility/Hospital: _____	
	Type of Birthplace: _____	If Home Birth: _____	<input type="checkbox"/> Delivered <input type="checkbox"/> Not Delivered <input type="checkbox"/> Unknown <input type="checkbox"/> Inferred	County: _____	
	Full Address/Location of delivery if not hospital: Street & Number _____		City _____	State _____	Zip Code _____
MOTHER I	Mother's Current Legal Name First _____ Middle _____ Last _____		Country of Birth: _____		
	Date of Birth: <u> </u> / <u> </u> / <u> </u> (MM/DD/YYYY)	Birthplace (State/Territory): _____	Social Security Number: _____		Requesting Social Security Number for Child? <input type="checkbox"/> Yes <input type="checkbox"/> No
	If unmarried, has Paternity Acknowledgment been signed in the hospital? <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unknown		Is the mother married? <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unknown <input type="checkbox"/> Refused		
	Mother's Name Prior to First Marriage First _____ Middle _____ Last _____		Date PA Signed: <u> </u> / <u> </u> / <u> </u> (MM/DD/YYYY)		
	Residence Address: Street & Number _____		County _____	City _____	State _____ Zip Code _____
	County _____	Country _____	Inside city limits? <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unknown		
Phone Number () _____		Years _____ Months _____ of current residence			
Mother's Mailing Address: Street & Number _____		<input type="checkbox"/> Same as Residence or enter below	County _____	State _____ Zip Code _____	
MOTHER II	Mother's Education Level: _____		History of Childhood distress in family? <input type="checkbox"/> Yes <input type="checkbox"/> No		
	Mother's Occupation: _____		Kind of business or industry: _____		
	Is mother of Hispanic origin or descent? Mexican/Mexican American/Nicarag. Puerto Rican Cuban *Other Spanish/Hispanic/Latina *Other (Specify) _____		<input type="checkbox"/> Yes <input type="checkbox"/> No	If yes, please circle below: <input type="checkbox"/> Unknown <input type="checkbox"/> Refused <input type="checkbox"/> Not Observable	
	Mother's Race (circle all that apply): White Asian Indian Chinese Filipino Japanese Korean Black/African American Vietnamese Native Hawaiian Guamanian/Cherokee Samoan *American Indian/Alaskan Native *Specify _____ Other Asian (Specify) _____		Other Pacific Islander (Specify) _____ Other (Specify) _____		

APPENDIX B

Parent/Guardian RSV Survey Instrument

Survey Questions

How often do you need to have someone help you when you read instructions, pamphlets, or other written material from your doctor or pharmacy?	1=never 2=almost never 3=sometimes 4=often 5=always
Did your premature infant have or ever had chronic lung disease, heart disease, or disease affecting airway clearance?	Y N
1. Do you have a premature infant between 29 and 32 week gestation?	Y N
2. Have your premature infant ever been diagnosed with RSV in the 1 st year of life?	
3. Did your premature infant have to be hospitalized for RSV?	Y N
4. Did your child receive RSV vaccination at less than 1 year of life?	Y N
5. Family Household:	
5a. How many people are in your household?	
5b. How many working adults are in your household?	1 2 3 4 5+ 1 2 3 4 5+
5c. Do you or the premature child receive Medicaid and/or private insurance?	Y N
5d. Family income?	
a. <20,000	
b. 20K-49K	
c. 50K-79K	
d. 80K-119K	
e. >120K	
6. Day care situation:	
6a. Do any of the siblings attend daycare or school?	Y N
6b. Does the premature infant attends or has ever attended daycare at less than 1 year of life?	Y N
6c. How often does he or she attend daycare?	Y N

7.RSV immunization:

7a.Would you or have you initiated vaccination for your premature infant for RSV?

Y N

7b.If you have initiated vaccination, did your premature infant receive first dose in hospital?

Y N

7c.How many doses did your baby receive?

Y N

7d.Did you receive the total recommended RSV doses for your premature infant?

Y N

7e.If you do not plan on vaccinating, why not?

i.Due to religious belief?

Y N

ii.Due to potential harm to child?

Y N

iii.Due to lack of exposure to disease?(circle one or more)no day care, no siblings in school or daycare, No one in home smokes.

Y N

iv. Due to (circle one or more) lack of access to health care provider, Transportation, unable to get adequate appointment time.

1 2 3 4 5

APPENDIX C

IRB Human Subjects Form

1. The purpose of the project and project background. To describe the research question and literature review.

In August of 2014, The American Academy of pediatrics updated the RSV policy guidelines for Palivizumab for premature infants. The objective of this project is to develop a framework to evaluate the health effects of the AAP policy change concerning premature infants 29-32 week gestational age. This project will also address some of the factors affecting immunization rates particularly the attitudes of parents concerning health benefits and harm of RSV immunization in Georgia and differences in the metropolitan Atlanta area.

2. Recruitment procedures and participant population. This section profiles the participants, exclusion criteria, how we will recruit and sensitive subjects, incentive information.

A sample of 400 women Of 29-32 gestational age infants will be randomly selected from birth certificate information in the 28 metro Atlanta counties in the pre- and post- policy change periods. The survey goal is to obtain 200 completed surveys from both Caucasian and African American mothers /guardians of premature infants in the pre- and post-policy periods.

3. Informed consent process.

We will mail a packet with survey, informed consent form and information. If the packet is not returned completed or undeliverable, we will contact the mother by phone.

4. Procedures and Methodology/ research protocol. A step-by step explanation of research activities.

(methods section)

5. Participants debriefing and feedback.

The participant will be given a feedback form for suggestions.

6. Potential risks to dignity, rights, health welfare of participants.

Potential risks to dignity will be minimal as this will be anonymous. The participant has the right to withdraw from the survey study at any time. This project has no health risk to the infant and mother.

7. Confidentiality and safeguards to minimize risk.

The sample will be obtained randomly and information organized by birth certificate number.

8. Study benefits.

The benefits of the study will provide insight into vaccination tendency and infant risk of 29-32 week gestational age infants. Also to assess if there is difference in initiation, completion and acquired infection in infants less than 29 weeks gestation pre- and post-policy change is a goal.

9. Researcher's qualifications and experiences.

The author is master's public health student under the supervision of thesis committee consisting of instructors with PHD and MD degrees.

10. Checklist: Human subjects, the use of surveys, consent forms.

To obtain a CITI certified research assistant, I will advertise through Public Health Program Schools. After obtaining phone numbers and address, we would send questionnaires to premature infant's mother concerning RSV vaccinations, attitudes of likelihood to vaccinate, family and siblings info. A follow-up phone call if survey was not received and mail another survey are some alternatives to boost low responses.

APPENDIX D

2x2 Tables for example 1 AAP change:

RSV vaccine initiation in infants less than 29 weeks gestational age, completion, and acquired infection RSV

1)

Vaccine initiation

	Y	N
Pre-policy	a	b
Post-policy	c	d

2)

Vaccine completion

	Y	N
Pre-policy	a	b
Post-policy	c	d

3)

Acquired RSV infection

	Y	N
Pre-policy	a	b
Post-policy	c	d

APPENDIX E

Example 2 Ongoing RSV Surveillance

Insurance status with RSV vaccine initiation, completion, and acquired RSV infection

1) Initiated vaccine

Insurance status	Y	N
Medicaid	a	b
Private	c	d
Uninsured	e	f

2) Completed vaccine

Insurance status	Y	N
Medicaid	a	b
Private	c	d
Uninsured	e	f

3) Acquired RSV infection

Insurance status	Y	N
Medicaid	a	b
Private	c	d
Uninsured	e	f