PROTOCOL

Title	Assessing Geographic Associations of Respiratory Syncytial Virus Spread and Nirsevimab Administration with Healthcare Utilization in Orange County
IRB Number	2409110
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Background Information and Rationale

Respiratory syncytial virus (RSV) is one of the leading causes of lower respiratory tract illnesses (LRTIs) in children.[1] The economic burden of RSV is significant, leading to thousands of medically-attended visits from the primary care office to the intensive care unit each year.[2] Risk factors for morbidity and mortality include age, prematurity, and certain chronic conditions such as chronic lung disease, immunosuppression, and congenital heart disease.[3] Social determinants of health (SDoH) and geographic location are being increasingly recognized as additional risk factors for poor outcomes for a variety of conditions, including RSV infections.[4–8]

Immunizations are well-known to be an effective strategy at mitigating disease incidence, prevalence, and burden.[9] Work has been initiated at multiple levels to track the spread of viral infections in order to determine appropriate timing and implementation of prevention efforts such as the influenza and SARS-CoV-2 vaccines.[10,11] Supply and cost-effectiveness of an immunization can affect how it is offered or recommended such as in limiting palivizumab to certain high-risk populations given high cost. Analysis of targeted distribution of palivizumab to medically high-risk children in Canada showed a greater reduction in the burden of RSV disease for that population while also leading to a possible spillover effect to those who were ineligible for the immunization.[12] Another study investigated the effects of carefully timing palivizumab to local epidemics; the model demonstrated reduced dosing of the palivizumab would have similar effectiveness as the standard dosing, leading to better cost-effectiveness.[13] Public health efforts to target the initial roll-out of COVID-19 vaccines to health care workers, seniors, and immunocompromised patients are well-known. Real-time geospatial analysis of vaccination gaps allowed for targeted distribution to underserved areas that could be culturally tailored to the neighborhood in one city.[14] Models in another study showed that vaccination uptake was key to vaccination prioritization strategies, demonstrating that targeted interventions are only effective if they lead to eventual vaccination.[15]

Increased attention and directed/targeted resources to underserved neighborhoods helps decrease utilization in multiple conditions.[16–19] Including geographic risk in public health planning can lead to more equitable distribution and uptake of immunizations.[15,20–26] Nirsevimab, a long-acting monoclonal antibody targeting RSV, is expected to be more widely available in the upcoming 2024-2025 RSV season to help prevent RSV morbidity and mortality.[3,27] With new widespread availability, it is unknown how this immunization will affect the incidence, spread, and clinical outcomes of RSV infections as well as the equity in vaccination distribution and uptake. This information will also be valuable in planning future targeted interventions to equitably increase immunization rates and improve clinical outcomes.

Study Objectives / Aims / Key Research Question

- Primary objective: to determine how positive RSV rates and nirsevimab immunization rates affect health system utilization defined as medically attended visits by census tract in Orange County
- Secondary objectives:
    - Locate the neighborhoods associated with high positive RSV rates in prior seasons and determine if they are the same each year or change
    - Compare health system data to county data to determine if infection clusters are similarly located
    - Compare locations of neighborhoods with high positivity rates and those with worse clinical outcomes and higher utilization
    - Identify gaps in equitable distribution of nirsevimab
    - Calculate immunization uptake by neighborhood and demographics
    - Quantify costs associated with nirsevimab uptake

Outcome Variables

Primary outcome: medically attended visit rate for RSV infection by census tract
Secondary outcomes by census tract for RSV infection: length of stay, acuity, average cost for RSV infection encounter

Study Population

Recruitment

Patients will be identified by querying electronic medical record for all visits (office, ED, hospital) for RSV infection or test or nirsevimab administration.

Study Eligibility

Inclusion Criteria

1) Patients of any age with a positive RSV PCR test from September 2013 – June 2025.

2) Patients eligible for nirsevimab (all infants in first year of life whose mother did not receive RSV vaccine at least 2 weeks prior to delivery and infants in the second year of life with certain high-risk chronic conditions including chronic lung disease and congenital heart disease) from September 2023 – June 2025.

3) Patients 21 years and younger for medically-attended RSV encounters

Exclusion Criteria

We will exclude patients with an unspecified home address (i.e., unhoused, in government custody, living in a group home, or no valid address) since a current address is necessary to evaluate the relationship to geographic location.

Study Site(s) & Sample Size

This is a single site study and will only take place at CHOC. The total estimated number of patient subjects at CHOC is approximately 5000**.**

Study Timelines

We anticipate accessing the medical record for data collection and verification during the project duration from approximately October 2024 through December 2026.

The data to be obtained will be from September 1, 2013 through June 30, 2025.

Research Methodology/Study Procedures

This is a retrospective comparative cohort study combining geographic data and patient data to assess disparities in RSV rates, health care utilization rates and immunization uptake rates by census tract in Orange County (see Data Collection and Management and Statistical Considerations sections for further details). The primary outcomes are 1) census tract RSV rates; 2) census tract immunization rates; and 3) healthcare utilization rates for the Orange County pediatric population age 0-2 years from September 2013 to June 2025. Data from CHOC patients tested and treated for RSV during the study period will be included to characterize the target patient population in more detail and to evaluate costs associated with RSV in Orange County. Publicly accessible Orange County Health Care Agency data on RSV rates for all ages by location will also be utilized for comparison to CHOC data.

Results from this study will be used to inform public health decision-making for pediatric immunization in Orange County. The results from this study may also be used to develop a follow-up study to address health disparities in nirsevimab administration and evaluate alternative strategies to improve immunization uptake in Orange County. Future studies may include simulation of immunization uptake strategies to assess their impact in mitigating RSV outbreak and/or machine learning algorithms to classify census tract RSV risk (H,M,L).

Data Collection & Management

Data Extraction from CHOC Cerner
An extraction form CHOC Cerner will be performed by CHOC Research Computational Science personnel for all CHOC patients 1) of any age with an RSV test performed at CHOC between September 2013 and June 2025 2) ages 0-2 with a nirsevimab administration and 3) ages 21 years and under with a medically-attended RSV encounter.
Specific Elements to be extracted:
Demographics: age at time of visit, date of birth, gender, race/ethnicity, insurance type, complete address which will be geocoded for geospatial analysis, primary language
Diagnoses: principal diagnosis, all secondary diagnoses (including SDoH diagnoses), and coded co-morbidities
Historical components: chief complaints, identified primary care provider, prior ED visits and admissions
Clinical Factors: level of acuity, RSV PCR test result
Medical interventions: nirsevimab administration, level of respiratory support (e.g., nasal cannula, high-flow nasal cannula, positive pressure, intubation), need for inotropic support
Administrative Data: visit type, admission bed type, overall charges, length of stay
All-cause returns to ED or re-admission within 30 days. For any ED or re-admission within 30 days, the record will be reviewed for reason of return and length of stay. If return is related to initial encounter, then any complications will be abstracted and charges obtained.

Informed Consent & HIPAA Authorization

We are requesting a waiver of informed consent and HIPAA authorization.

Risk Benefit Analysis

Risks

The study involves almost no risk to the patients as it is a retrospective review. The only theoretical risk is potential loss of confidentiality, which is no greater than what would be associated with routine clinical care. Processes are noted in the Safety Management section below to minimize this risk.

Benefits

Identifying geographic areas with increased RSV rates can help identify resource needs and target prevention efforts. The study may lead to improved patient care delivery, resource utilization, and patient safety.

Safety Management

Safety and adverse events are not expected with this protocol. Any unanticipated problems involving risks to the subjects or others during the course of this study will be reported to the IRB. There is potential risk with accessing PHI, and the following plan will be used to protect human subjects from improper use or disclosure of PHI:

a. All CHOC study personnel are trained specifically on issues related to confidentiality (including HIPAA regulations). Only study personnel will have access to CHOC data.
b. All CHOC Cerner data necessary for this study will be extracted from the CHOC Cerner database by CHOC Research Computational Science personnel. Extracted data will be imported into and housed in a REDCap database for purposes of data management. The RedCap database will contain PHI including patient identifiers, encounter numbers, medical record numbers, date of birth, and dates related to treatment. Only the study investigators will have access to these records for purposes of data management, data merging with PHIS CHOC data, and analysis.
c. After data extraction is complete, the CHOC medical record numbers will be de-identified by assigning consecutive, ascending nominal study numbers. A separate data file will be created that links CHOC medical record numbers and date of birth with the assigned study numbers. This data file will only be available to the PI and saved in a password-protected file that is also encrypted and stored on a secure server.
d. The REDCap data file will only be available to study personnel and is saved in a password-protected file on a HIPPA-compliant secure cloud server.
e. All data will be available to the statisticians for the purpose of data cleaning, preparation, management, analysis, summarization, matching/merging, and extraction for purposes of analysis and sub-analysis.
f. All data will be electronic data and will be stored in REDCap on a password-protected cloud-based HIPPA-compliant secure server.
g. Data will be reported summarized for reporting purposes in aggregate form only without any identifying information.
h. Personal information recorded will be limited to what is essential to the research.
i. All data collected will be managed in compliance with CHOC research policy regarding data file management and preservation for regulatory/audit purposes.
j. Data management is designed to ensure the highest quality data possible and the highest levels of data security. Data management activities will be ongoing and will include evaluation for missingness, overall reliability and completeness. Extraction, merging, and matching datafiles will be performed by experienced personnel of the CHOC Research Institute and includes but is not limited to the following activities: programming, data pre-processing/cleaning, data restructuring, data quality control procedures, quality assurance, adherence to confidentiality protocols, and the development of data files for statistical analysis.
k. As a retrospective cohort study, a waiver of HIPPA authorization to utilize electronic health records will be requested as part of the IRB application. This study is low risk with the most serious risk related to an unauthorized data breach. Since experienced CHOC research personnel are the primary personnel responsible for data extraction and management, and CHOC Research policies and procedures will be followed to minimize the risk of breach, risk of unauthorized data breach are minimal.

l. The protected health information will not be reused or disclosed to another person or entity, except as required by law, for authorized oversight of the research study. Given the data that we propose to extract, it is not reasonably foreseeable that we will access or collect data requiring report to other officials or ethically requiring action.
m. No change in provider care is a component of this study. Data developed for purposes of proposed targeting will not be utilized directly as part of the study. Study conclusions and recommendations regarding the potential impact of future targeting will not be implemented directly as a part of this study. Conclusions from this study may be used in the future to improve immunization uptake in Orange County but that decision will follow current CHOC policies and procedures regarding public health decision-making. No change in current immunization administration is included as a component of this study. CHOC providers will continue to deliver standard of care regarding immunization for RSV which for the purposes of this study is the administration of nirsevimab to the Orange County pediatric population age 0-18 years as directed by current CHOC policy and procedure. Consent for that administration of nirsevimab follows the normal standard of care and CHOC treatment protocol for the administration of immunizations to the public and is not a part of this study. This study only collects data related to RSV rates, nirsevimab administration, and CHOC patients tested for RSV at CHOC. No study personnel will perform immunization administration as a part of this study although study team members are CHOC providers and may participate in the care and treatment of CHOC patients who may also be included in the study cohort.

Statistical Considerations

Data Sources: Data for this study will be normed based on population data by census tract available from the U.S. Census Bureau area-level socioeconomic data which will include de-identified aggregated data for children ages 0-18 years. Other available data from the Orange County Health Care Agency and other open-access public health data such as the Child Opportunity Index[28] or the California Healthy Places Index[29] may also be collected as needed and available to provide current and historical estimates of RSV rates, immunization rates, and composite socioeconomic data in Orange County. If feasible, data for CHOC Cerner patients may also be matched to patient data from the Pediatric Health Information System (PHIS) database[30] for costs and other administrative data as needed. Based on previous experience with both databases, access to both CHOC Cerner and PHIS will facilitate data extraction and improve data reliability since PHIS can be utilized to confirm CHOC Cerner data reliability and provide patient data not as easily accessible via CHOC Cerner, such as utilization, medication, and cost data.

Study Design: This study utilizes a retrospective comparative public health cohort design. This study design utilizes both the census tract and the patient as the unit of analyses. For comparison among census tracts, patient data will be summarized to the census tract level using the patient's address or by matching patient identifiers to census tract patient cohorts by other identifiers.

Statistical Analyses: Demographic and clinical characteristics of the CHOC patient population across all census tracts in Orange County will be described overall by percentage with defined trait for categorical and mean (SD) or median [IQR] for continuous factors. Comparisons among census tracts by relevant demographics will also be described by percentage with defined trait for categorical and mean (SD) or median [IQR] for continuous factors. Rates may also be summarized by quintiles to further assess disparities. Significant differences in summary demographic characteristics (and quintiles) by tract, healthcare utilization rates, RSV rates, and immunization uptake rates will be assessed using independent t-test, Chi-square test and Mann-Whitney U test, as applicable.

Geospatial analysis of RSV rates and nirsevimab administration in the Orange County pediatric population will also be performed to describe RSV rates, healthcare utilization rates, and uptake of vaccine administration by census tract utilizing ArcGIS®, a geographic software information system from Environmental Systems Research Institute. ArcGIS is an international supplier of geographic information system (GIS) software (information at: https://www.arcgis.com/index.html).

Statistical significance will be set at $\alpha = 0.05$ level. All analyses will be conducted using SPSS 29 (IBM: Armonk. NY).

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