Health & Place 45 (2017) 46–54

Contents lists available at ScienceDirect

Health & Place

journal homepage: www.elsevier.com/locate/healthplace

The impact of temperature and relative humidity on spatiotemporal patterns of infant bronchiolitis epidemics in the contiguous United States

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A R T I C L E I N F O

Keywords:
RSV
Climate
Respiratory
Seasonal

A B S T R A C T

Infant bronchiolitis is primarily due to infection by respiratory syncytial virus (RSV), which is highly seasonal. The goal of the study is to understand how circulation of RSV is impacted by fluctuations in temperature and humidity in order to inform prevention efforts. Using data from the Military Health System (MHS) Data Repository (MDR), we calculated rates of infant bronchiolitis for the contiguous US from July 2004 to June 2013. Monthly temperature and relative humidity were extracted from the National Climate Data Center. Using a spatiotemporal generalized linear model for binomial data, we estimated bronchiolitis rates and the effects of temperature and relative humidity while allowing them to vary over location and time. Our results indicate a seasonal pattern that begins in the Southeast during November or December, then spreading in a Northwest direction. The relationships of temperature and humidity were spatially heterogeneous, and we find that climate can partially account for early onset or longer epidemic duration. Small changes in climate may be associated with larger fluctuations in epidemic duration.

1. Introduction

Bronchiolitis is a lower respiratory tract infection (LRTI) that is predominantly caused by respiratory syncytial virus (RSV) among infants during the winter virus season (McNamara and Smyth, 2002). RSV is responsible for between 50% and 80% of bronchiolitis in infants. An estimated 2.3% of neonatal (age 0–27 days) deaths and 6.7% post-neonatal (age 28–364 days) deaths were due to RSV related lower respiratory infections (Lozano et al., 2013). For children aged 5 and younger, an estimated 3.4 million hospitalizations per year are related to RSV worldwide, including between 66,000 and 199,000 deaths (Nair et al., 2010). Additionally, infant bronchiolitis has been shown to have a strong causal link with the later development of childhood asthma (Heymann et al., 2004; Wu et al., 2008). Despite the high prevalence and the significant morbidity and mortality, treatment for bronchiolitis is limited to supportive care, and an effective vaccine has not yet been developed. Monthly administration of immunoprophylaxis is the only available preventive measure. However, immunoprophylaxis is very expensive, with expected costs during one RSV season between $9939 and $13,500 for children less than two years old (Hampp et al., 2011). Thus understanding factors which impact viral spread is another option for pursuing targeted infection prevention.

RSV circulation follows distinct annual patterns similar to influenza, peaking primarily between November and March in the northern hemisphere and during April and September in the southern hemisphere (Noyola and Mandeville, 2008; Taylor et al., 2016; Walton et al., 2010; Welliver Sr, 2007). In the tropics, RSV circulation typically corresponds with the rainy season, though the seasonal peak is not pronounced (Chan et al., 2002). In North America, the annual epidemic is typically found earliest in the southern coastal areas in September and October and then is thought to proceed generally westward and northward (Control and Prevention, 2013; Pitzer et al., 2015; Stensballe et al., 2003). A national study by the Centers for Disease Control and Prevention indicated that the peak timing of RSV epidemics can range between December 3rd and March 17th, depending on location (with seasons ending as late as May 5th) (Control and Prevention, 2013).

The reasons for these patterns, potential for year-specific fluctua-

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http://dx.doi.org/10.1016/j.healthplace.2017.02.010
Received 25 July 2016; Received in revised form 9 December 2016; Accepted 24 February 2017

tions in RSV epidemics, and how they correspond with the timing of location-specific rates of immunoprophylaxis administration are unknown. For instance, models suggest that climate and demographic factors influence RSV transmission and host susceptibility (Bradley et al., 2005; Gürkan et al., 2000; Welliver Sr, 2007; Yusuf et al., 2007). The magnitude of the association between factors that influence RSV dynamics and ecology likely varies across the United States. This is evident as studies of northern climates suggest that temperature is highly correlated with bronchiolitis and RSV rates. However more moderate, coastal climates in the US also experience peaks of bronchiolitis in winter. Even within a single US state, epidemic curves can considerably between cities where climates are very similar (Sloan et al., 2013). While immunoprophylaxis is typically administered between November and March, local rates and timing of administration also vary by location.

In order to facilitate accurate prediction of bronchiolitis rates as a necessary precursor to more effective prevention strategies, variation across the United States must be better understood. While the ubiquitous annual circulation of RSV is difficult to measure in infant populations across large geographic areas, it is possible to track bronchiolitis in infants using medical claims data. In this study, we performed the largest and most geographically diverse study of temperature, climate and infant bronchiolitis rates conducted to date. The goal of this study was to model variation in spatiotemporal patterns of infant bronchiolitis rates in a nationwide health care database in the United States, and to understand the influence of temperature and humidity on those rates.

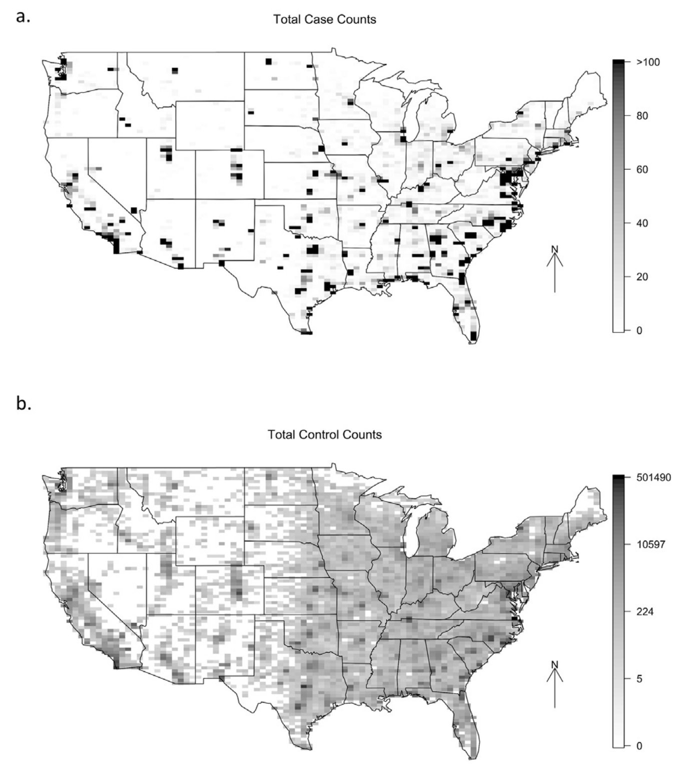

Fig. 1. (a) Total counts of the number of bronchiolitis cases and (b) controls from the MHSD.

2. Methods

2.1. Database/population

Infants covered by the Department of Defense (DoD) Military Health System (MHS) and whose data are available in the MHS Data Repository (MDR) were studied. The MDR contains data for the entire MHS, which serves all active duty and retired military personnel and their dependents. The MDR contains data on almost 10 million covered individuals (including over 2300 births per week) and incorporates all the administrative and pharmacy data derived from visits to military medical facilities as well as any civilian network visits billed to the Department of Defense. Approximately 40% of the births and outpatient visits and 25% of the inpatient visits occur in military hospitals and clinics with the balance of care being provided by civilian facilities. Covered individuals live across the United States and are demographically representative of the US population as a whole. We used medical codes for diagnoses and location data for all infant bronchiolitis events (cases) and location data for all other infants (controls).

Inclusion criteria were infants born in the contiguous United States between January 1, 2003 and June 30, 2013 that were enrolled in the MHS between birth and 1 year of age. Cases were defined as infants diagnosed with bronchiolitis (ICD-9 codes: 466.11, 466.19, 480.1, 0.79.6). Note that 480.1 is a code that refers to pneumonia due to RSV, not bronchiolitis, but which is included as it is a lower respiratory infection due to RSV. We retrieved necessary medical claims and location data for all infant bronchiolitis events (cases) and location data for all other infants (controls). Due to the sensitive nature of these data, residence locations were jittered and birthdates and healthcare visits were skewed to protect patient's privacy. Confidentiality rules prevent disclosing the actual distances and number of days.

The study was approved by the Institutional Review Board (IRB) of both the Naval Medical Center Portsmouth and Brigham Young University.

2.2. Grid cell aggregation

For purposes of statistical analysis, case and control counts were aggregated to the 5396 regularly spaced, spatial grid cells shown in Supplemental Fig. 1 at the monthly time scale. Each grid cell in Supplemental Fig. 1 is approximately 17 miles (27 km) in the east-west direction and 30 miles (48 km) in the north-south direction. For controls, we only have data on infants born from January 1, 2003 forward. Therefore, we don't have a good value for the number of control infants less than one year old until January 2004 (i.e. we use birth data in 2003 to calculate the number of controls for 2004). For this analysis, we consider the number of bronchiolitis cases and controls that fall in each of the 5396 grid cells for each month beginning July 1, 2004 to June 30, 2013 resulting in $5396 \times 12 \times 9 = 582{,}768$ correlated data points.

The spatial grid shown in Supplemental Fig. 1 was chosen because the spatial resolution of 5396 grid cells is sufficiently coarse to nullify the spatial uncertainty associated with the jittering of the spatial locations in the data. In other words, given the jittering distance for each location, we are able to locate, within a probability of 0.0001, the grid cell in which the case (or control) lies. Additionally, this spatial resolution is sufficiently high for purposes of this study, while still being small enough to facilitate a computationally reasonable spatio-temporal analysis (for details, see the Section 2.4 below).

One month was chosen as a sufficiently high temporal resolution to produce scientifically interesting results while still coarse enough to prevent the data from being too sparse to calculate rates. A smaller temporal resolution on the order of two weeks would produce case counts as low as 30 for the entire contiguous US, which would jeopardize de-identification.

2.3. Predictors: temperature and humidity data

As a key focus of this study was the impact of climate on bronchiolitis rates, we utilized monthly average temperature data from the National Climatic Data Center (NCDC). The temperature data consists of 7,945,096 daily average temperatures at different land stations throughout the United States, over the study period. For relative humidity, we have 73,705 observations, also gathered at