**Supplemental Digital Content 1.**

**Study Design, Setting, and Participants**

The present analysis combines data from two multi-center, multi-year prospective cohort studies of infants with severe bronchiolitis. Using a similar protocol, one study enrolled subjects during 2007-2010, while the other enrolled during 2011-2014. Both studies were performed as part of the Multicenter Airway Research Collaboration (MARC). MARC is a program of the Emergency Medicine Network (EMNet) (www.emnet-usa.org), a research collaboration with almost 250 participating hospitals. The study design, setting, participants, and methods of data collection used in the studies have been reported previously.1-4

In brief, the 2007-2011 study – called the 30th Multicenter Airway Research Collaboration (MARC-30) – was performed at 16 sites across 12 U.S. states during three consecutive bronchiolitis season (from November 1 through March 31) in 2007-2010 (**see table, Supplemental Digital Content 7**).1,2 The study enrolled children (<2 years of age) hospitalized with the diagnosis of bronchiolitis by an attending physician, with the ability of the parent/guardian to give informed consent. We enrolled a target number of consecutive patients from the inpatient wards and the intensive care unit (ICU) with an aim to enroll 20% of the cohort from ICUs. Bronchiolitis was defined by the American Academy of Pediatrics guideline – acute respiratory illness with some combination of rhinitis, cough, tachypnea, wheezing, crackles, and retractions.5 The study excluded children who were transferred to a participating hospital >48 hours after the original hospitalization.

The 2011-2014 study – called the 35th Multicenter Airway Research Collaboration (MARC-35) – was performed at 17 sites across 14 U.S. states (**see table, Supplemental Digital Content 2**).3,4 Using the similar standardized protocol as the MARC-30 study, MARC-35 enrolled infants (aged <1 year) hospitalized with an attending physician diagnosis of bronchiolitis during three consecutive bronchiolitis season (from November 1 to April 30) in 2011-2014. Unlike MARC-30, MARC-35 had no over-representation of ICU cases. The study excluded infants who were transferred to a participating hospital >24 hours after the original hospitalization, those who were consented >24 hours after hospitalization, or those with known heart-lung disease, immunodeficiency, immunosuppression, or gestational age <32 weeks. In both studies, all patients were treated at the discretion of the treating physician. The institutional review board at each of the participating hospitals approved the studies. Written informed consent was obtained from the parent or guardian.

**Data Collection and Measurement**

Investigators conducted structured interview and medical record review that measured patient characteristics and clinical data, such as in-hospital management and disposition. All data were reviewed at the EMNet Coordinating Center (Boston, MA, USA), and site investigators were queried about missing data and discrepancies identified by manual data checks.

In addition to the clinical data, investigators collected nasopharyngeal aspirates within 24 hours of hospitalization by using a standardized protocol.1-4 Designated site personnel were trained using a lecture, written instructions, and video. All of the sites used the same collection equipment (Medline Industries, Mundelein, IL, USA). Once collected, the NPA sample was added to transport medium at a 1:1 ratio. The samples were immediately placed on ice within 1 hour of collection, and then stored at –80oC within 24 hours of collection.

**Polymerase Chain Reaction (PCR) Assay**

Identification of respiratory pathogens was performed by using singleplex or duplex two-step real-time PCR (rtPCR) at Baylor College of Medicine (Houston, TX, USA). Real-time reverse transcriptase-PCR was used for the detection of RNA respiratory viruses, including RSV (types A and B),6,7 rhinovirus,8 coronaviruses (NL-63, OC-43, HKU1,9,10 and 229E), human metapneumovirus (hMPV),7 parainfluenza viruses (types 1, 2 and 3),11 enteroviruses,12 and influenza viruses (types A and B, and 2009 novel H1N1).7,13,14 rtPCR was also used for the detection of DNA pathogens which included adenovirus,15human bocavirus type 1,16 *Mycoplasma pneumoniae*,17 and *Bordetella pertussis*.18 Details of the primers and probes have been described in the Online Supplement. All rtPCR assays were tested in duplicate and samples with incongruent values (one well positive) were retested. To reduce carryover contamination, sample preparation, RNA/DNA extraction, cDNA and amplification were performed in separate areas. All PCR runs had extraction and reagent positive and negative controls.

**Statistical Analysis**

In the current analysis, we analyzed the data of infants (<1 year of age) from the MARC-30 and MARC-35 cohorts. We used descriptive statistics to summarize the patient characteristics, clinical course, and detected respiratory pathogens (e.g., proportion, median with interquartile range [IQR]). We also compared the likelihood of having each of the five most common pathogens (with a detection likelihood of >5%) between the U.S. census regions (Northeast, Midwest, South, West)19 by using chi-squared test. Given the potential clinical importance, RSV was stratified into subtypes A and B.20 To examine the region-×-month (compilation of study years) interactions with regard to the likelihood of having each virus, we used random-effects model adjusting for hospitalization year and patient clustering within hospitals, as well as likelihood ratio test. Analyses used R version 3.4. All P-values were two-tailed, with P<0.05 considered statistically significant.

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