Respiratory Syncytial Virus–Associated Hospitalizations Among Young Children: 2015–2016

Brian Rha, MD, MSPH,[a] Aaron T. Curns, MPH,[a] Joana Y. Lively, MPH,[a,b] Angela P. Campbell, MD, MPH,[c] Janet A. Englund, MD,[d] Julie A. Boom, MD,[e,f] Parvin H. Azimi, MD,[g] Geoffrey A. Weinberg, MD,[h] Mary A. Staat, MD, MPH,[i] Rangaraj Selvarangan, BVSc, PhD,[j] Natasha B. Halasa, MD, MPH,[k] Monica M. McNeal, MS,[i] Eileen J. Klein, MD, MPH,[d] Christopher J. Harrison, MD,[j] John V. Williams, MD,[l] Peter G. Szilagyi, MD, MPH,[m] Monica N. Singer, MD, MPH,[g] Leila C. Sahni, PhD, MPH,[e] Daniella Figueroa-Downing, MPH,[a,n] Darius McDaniel, MSPH,[a,o] Mila M. Prill, MSPH,[a] Brett L. Whitaker, MS,[a] Laura S. Stewart, PhD,[k] Jennifer E. Schuster, MD, MSCI,[j] Barbara A. Pahud, MD, MPH,[j] Gina Weddle, DNP, RN, CPNP-AC/PC,[j] Vasanthi Avadhanula, PhD,[p] Flor M. Munoz, MD,[e,f,p] Pedro A. Piedra, MD,[e,f,p] Daniel C. Payne, PhD,[a] Gayle Langley, MD, MPH,[a] Susan I. Gerber, MD[a]

abstract

BACKGROUND: Respiratory syncytial virus (RSV) is a major cause of hospitalized acute respiratory illness (ARI) among young children. With RSV vaccines and immunoprophylaxis agents in clinical development, we sought to update estimates of US pediatric RSV hospitalization burden.

METHODS: Children <5 years old hospitalized for ARI were enrolled through active, prospective, population-based surveillance from November 1, 2015, to June 30, 2016, at 7 US pediatric hospital sites. Clinical information was obtained from parent interviews and medical records. Midturbinate nasal and throat flocked swabs were collected and tested for RSV by using molecular diagnostic assays at each site. We conducted descriptive analyses and calculated population-based rates of RSV-associated hospitalizations.

RESULTS: Among 2969 hospitalized children included in analyses, 1043 (35%) tested RSV-positive; 903 (87%) children who were RSV-positive were <2 years old, and 526 (50%) were <6 months old. RSV-associated hospitalization rates were 2.9 per 1000 children <5 years old and 14.7 per 1000 children <6 months old; the highest age-specific rate was observed in 1-month-old infants (25.1 per 1000). Most children who were infected with RSV (67%) had no underlying comorbid conditions and no history of preterm birth.

CONCLUSIONS: During the 2015–2016 season, RSV infection was associated with one-third of ARI hospitalizations in our study population of young children. Hospitalization rates were highest in infants <6 months. Most children who were RSV-positive had no history of prematurity or underlying medical conditions, suggesting that all young children could benefit from targeted interventions against RSV.

[a]*Division of Viral Diseases and* [c]*Influenza Division, Centers for Disease Control and Prevention, Atlanta, Georgia;* [b]*IHRC, Inc, Atlanta, Georgia;* [d]*Seattle Children's Hospital, Seattle, Washington;* [e]*Texas Children's Hospital, Houston, Texas;* [f]*Departments of Pediatrics and* [p]*Molecular Virology and Microbiology, Baylor College of Medicine, Houston, Texas;* [g]*University of California, San Francisco Benioff Children's Hospital Oakland, Oakland, California;* [h]*Department of Pediatrics, University of Rochester School of Medicine and Dentistry, Rochester, New York;* [i]*Division of Infectious Diseases, Department of Pediatrics, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio;* [j]*University of Missouri-Kansas City School of Medicine, Children's Mercy, Kansas City, Missouri;* [k]*Vanderbilt University Medical Center, Nashville, Tennessee;* [l]*University of Pittsburgh Medical Center Children's Hospital of Pittsburgh, Pittsburgh, Pennsylvania;* [m]*Department of Pediatrics, UCLA Mattel Children's Hospital, University of California, Los Angeles, Los Angeles, California;* [n]*P3S Corporation, San Antonio, Texas; and* [o]*Maximus Federal, Atlanta, Georgia*

WHAT'S KNOWN ON THIS SUBJECT: Respiratory syncytial virus (RSV) infection is a major cause of hospitalization among young children. The US pediatric burden of hospitalized RSV is substantial, with the most recent prospective population-based estimates of burden coming from 3 counties in 2000–2005.

WHAT THIS STUDY ADDS: During 2015–2016, prospective population-based surveillance over a broader geographic area detected RSV in one-third of acute respiratory illness hospitalizations in our study population of young US children and yielded updated burden estimates that should help inform RSV-specific intervention strategies.

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Respiratory syncytial virus (RSV) is a major cause of pediatric acute respiratory illness (ARI) hospitalizations in the United States.[1–3] The burden of RSV-associated hospitalizations among US children is substantial on the basis of estimates derived from administrative databases[4–8] and previous prospective surveillance.[1,2] The most recent prospective population-based estimates of hospitalized RSV burden among young US children were from 3 counties in 2000–2005, with a rate of 3 hospitalizations per 1000 children <5 years old and higher rates among young infants.[1,2]

Currently, there are no licensed RSV vaccines, and only one RSV monoclonal antibody product (palivizumab) is available for immunoprophylaxis in a limited high-risk infant population.[9] With vaccine candidates and additional immunoprophylaxis products targeting young infants and children in clinical development, updated burden estimates are particularly important.[10,11] We herein report a broader multisite update of the burden and clinical characteristics of RSV-associated hospitalizations using active, prospective surveillance conducted at 7 pediatric medical centers during the 2015–2016 season through the Centers for Disease Control and Prevention's (CDC) New Vaccine Surveillance Network.[3]

METHODS

Study Design

Inpatient surveillance was conducted at 7 pediatric medical centers from November 1, 2015, to June 30, 2016, in Rochester, New York; Cincinnati, Ohio; Nashville, Tennessee; Kansas City, Missouri; Houston, Texas; Seattle, Washington; and Oakland, California. Children <5 years old were eligible for enrollment if they resided within each hospital's surveillance area, had an illness duration <14 days, and were enrolled within 48 hours of admission for an ARI-related condition (Supplemental Table 5). Children were excluded if they had a known nonrespiratory cause for hospitalization, had fever and neutropenia from chemotherapy, were discharged from a hospital in the previous 4 days, were transferred from another hospital after an admission of >48 hours, had never been discharged from the hospital after birth, or had previously enrolled in this study <14 days before their current admission. Study staff identified eligible children 5 to 7 days per week; each surveillance day covered admissions for a 24-hour period.

Institutional review board approvals were obtained at the CDC and at each site. Informed written consent was obtained from parents and/or guardians of eligible children for participation in standardized parent and/or guardian interviews, medical chart review, and collection and testing of midturbinate nasal and throat swabs.

Patient and Laboratory Data

Parent and/or guardian interviews for all children included information regarding patient demographics (including race and/or ethnicity), history of current illness, and social history; among children <2 years old, prematurity (<37 weeks' gestation), gestational age at birth, and receipt of palivizumab during the 2015–2016 season were also assessed by interview. Chronic comorbid conditions, clinical interventions, and outcomes (including receipt of any supplemental oxygen above baseline during clinical care, ICU admission, and mechanical ventilation) were assessed through a standardized medical chart review.

Midturbinate nasal and throat flocked swabs were obtained and combined when both available and placed in universal transport media. For intubated patients, tracheal aspirates were accepted as alternatives to throat swabs. Specimens were transported to each site laboratory and stored at 2°C to 8°C until processed (within 72 hours). Specimens underwent testing at each site by commercial or institution-specific in-house reverse transcription polymerase chain reaction assays for RSV and other respiratory pathogens, including influenza A and B, human metapneumovirus, human parainfluenza viruses (HPIVs) 1 to 3, rhinoviruses and enteroviruses, and adenovirus. Diagnostic assay methods varied by site and included Luminex NxTAG Respiratory Pathogen Panel (in Cincinnati, Kansas City, and Oakland),[12] BioFire FilmArray Respiratory Panel (in Seattle),[13] Applied Biosystems TaqMan Array Microfluidic Card (in Rochester),[14,15] and in-house real-time reverse transcription polymerase chain reaction assays (in Houston[16,17] and Nashville[14,18]). All sites conducted CDC-sponsored proficiency testing to ensure the validity and consistency of results for all viral detections across sites.

Data Analyses

RSV infection was defined by a positive result from study-initiated RSV testing. Patients with inconclusive RSV test results due to insufficient specimen quality (as determined by assay controls) were excluded from analyses. For descriptive analyses, comparisons of patient characteristics by RSV status were performed by using χ^2 tests, and multivariable logistic regression analysis was used among patients who were RSV-positive to assess independent associations with the following clinical outcomes after adjusting for study site and patient age: ICU admission (regardless of the receipt of supplemental oxygen) and supplemental oxygen administration among non-ICU admissions.

Descriptive analyses included all enrolled patients, but population-based RSV-associated hospitalization rate calculations were restricted to residents of the specific counties for which additional population and care-seeking practices information was available. By site, these included Monroe County, New York (Rochester); Hamilton County, Ohio (Cincinnati); Davidson County, Tennessee (Nashville); Jackson County, Missouri (Kansas City); Harris, Fort Bend, Montgomery, Brazoria, Galveston, Liberty, Waller, and Chambers counties, Texas (Houston); King County, Washington (Seattle); and Alameda County, California (Oakland). Site-specific and overall network rates were calculated from the weighted number of RSV hospitalizations divided by the population <5 years of age for these counties multiplied by 1000[1–3]; rates were also calculated by age group, gestational age (for children <2 years old), sex, and race and/or ethnicity groups. For each of these site-specific county areas, population denominator data were from the 2016 US bridged-race estimates[19]; denominators by gestational age were determined by applying the proportion of births by gestational age from the 2013–2016 US natality data to the 2016 bridged-race estimates, restricted to children <2 years old.[20–23] The observed number of hospitalizations was weighted to account for any weeks in which sampling was <7 days per week, the number of eligible children not enrolled, and the market share (ie, the estimated proportion of ARI hospitalizations captured by each hospital in their respective specified county areas, generated by each site by comparing their hospitalization data for ARI-related conditions to county-based data). Rates (overall and by demographic subset) were calculated with 95% confidence intervals (CIs) determined by bootstrap percentiles based on 1000 bootstrap samples for each rate.[24] Rate ratios and 95% CIs were also obtained by bootstrap methods and used to identify significant differences in rates. When comparing 2 rates, rate ratio CIs that did not cross 1 indicated that the rates were significantly different.

RESULTS

Study Population and RSV Detections

During the 2015–2016 surveillance period, 3001 (64%) of 4716 eligible children were enrolled (Fig 1), of whom 2983 (>99%) had study-specific respiratory specimens collected and tested for RSV. Among 2969 with conclusive RSV testing results, 1043 (35%) were RSV-positive. Codetected virus cases in 132 patients who were RSV-positive (13%) included 92 (9%) rhinovirus and enterovirus, 28 (3%) adenovirus, 5 (<1%) influenza, 4 (<1%) human metapneumovirus, 3 (<1%) HPIV-3, and 2 (<1%) HPIV-1.

RSV was detected throughout the surveillance period from November 1, 2015, to June 28, 2016 (Fig 2). Overall, the proportion of RSV detections among patients with ARI was highest in December (52%), January (52%), and February (47%) and lowest in June (4%). The proportion of patients who were RSV-positive varied by site (Table 1), as did the magnitude and timing of peak RSV proportion positivity, ranging from 42% to 69% and occurring from November to February (Fig 2).

Demographics and Social History

Among 1043 hospitalized children who were RSV-positive, 587 (56%) were male, 903 (87%) were <2 years old, 526 (50%) were <6 months old, and 342 (33%) were <3 months old (Table 1). Race and ethnicity information, summarized in Table 1, revealed that 71% of children who were RSV-positive were reported as having non-Hispanic or non-Latino (NH) ethnicity, of whom 59% were reported as white and 25% as African American. Most children who were infected with RSV had public insurance (60%). Interviews revealed that 79% had a history of breastfeeding of any duration, 25% lived with household members who smoked, and 59% had a maternal education of high school or less (Table 2). Among all hospitalized children with ARI, children who were RSV-positive were generally younger than children who were RSV-negative (Table 1).

Underlying Medical Conditions and Prematurity

Chronic comorbid conditions were documented in 21% of children who were RSV-positive, including 11% with chronic lung conditions, 4% with congenital heart disease, and 4% with neurologic and/or neuromuscular conditions (Table 2). Among 903 children <2 years old who were RSV-positive, parental report revealed that 162 (18%) were born preterm (median of 34 weeks' gestational age [WGA]) and 21 (2%) received any palivizumab during the 2015–2016 season. Those reporting preterm birth included 70 (8%) at 35 to 36 WGA, 50 (6%) at 32 to 34 WGA, 18 (2%) at 29 to 31 WGA, 19 (2%) at <29 WGA, and 5 (1%) with no available WGA information (Table 3). Among all children who were RSV-positive, 339 (33%) had a chronic comorbid condition or were <2 years old with a history of prematurity (Table 2). Children who were RSV-positive were less likely to have a comorbid condition or history of prematurity (33%) than children who were RSV-negative (46%; $P < .001$).

Clinical Outcomes

The median length of stay for subjects who were RSV-positive was 2 days (interquartile range 1–3 days); 718 (69%) received supplemental oxygen, 182 (17%) were admitted to an ICU, and 27 (3%) required mechanical ventilation; there were no deaths (Table 2). Children who were RSV-

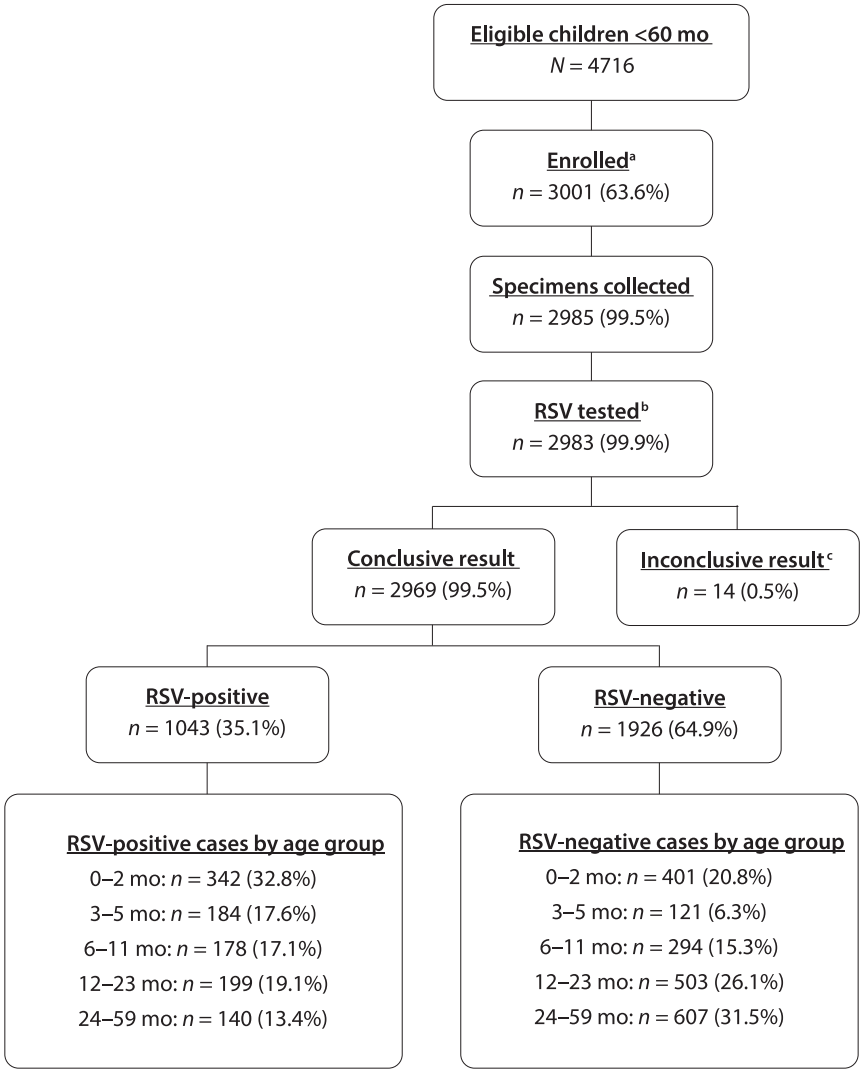

FIGURE 1

Enrollment and test results. [a] The most common reasons for nonenrollment included declination (50%), parent and/or guardian unavailability (20%), patient discharge before consent could be obtained (17%), and language barriers to consent (9%). Enrollment rates were similar by sex and insurance status but varied by age and race and/or ethnicity, with rates decreasing with increasing age (67% among 0- to 11-month-old children decreasing to 58% among 24- to 59-month-old children; $P < .001$), and were lowest among other (ie, not white or African American) NH children (56%). Hispanic or Latino children had the highest enrollment rate (70%; $P < .001$), whereas rates were similar between NH white (64%) and NH African American (63%) children. [b] Of 2983 children with RSV-tested respiratory specimens, 2846 (95%) provided combined midturbinate nasal and throat specimens, 97 (3%) provided midturbinate nasal specimens only, and 20 (<1%) provided throat specimens only; tracheal aspirates were collected from 20 (<1%) patients, either alone ($n = 4$) or with concurrent upper respiratory specimen ($n = 16$). [c] Inconclusive RSV test results were due to insufficient specimen quality (as determined by assay controls).

positive were more likely to require supplemental oxygen (69% vs 50%; $P < .001$) or ICU admission (17% vs 13%; $P = .002$) than children who were RSV-negative.

The characteristics of patients who were RSV-positive were further assessed for associations with ICU admission or receipt of supplemental oxygen for non-ICU admissions. Initial univariate analyses were used to identify significant study site differences for both outcomes ($P < .001$). Subsequent multivariable analyses were adjusted for age and study site (Supplemental Tables 6 and 7). Children who were RSV-positive who were outside the 12- to 23-month age group were more likely to be admitted to the ICU compared with those 12 to 23 months old (0–2 months: adjusted odds ratio [aOR] = 2.4 [95% CI: 1.4–4.1]; 3 to 5 months: aOR = 2.2 [95% CI: 1.2–4.1]; 6 to 11 months: aOR = 2.1 [95% CI: 1.1–3.8]; 24 to 59 months: aOR = 2.6 [95% CI: 1.4–4.9]); these differences remained statistically significant when including having any comorbid condition in the model. Those with a comorbid condition or history of prematurity were more likely to be admitted to the ICU than those who did not (aOR = 1.5 [95% CI: 1.1–2.2]). Among patients who were RSV-positive not admitted to the ICU, congenital heart disease was more common among those administered supplemental oxygen compared with those with no supplemental oxygen receipt (aOR = 2.5 [95% CI: 1.1–5.7]). In addition, NH African American children were less likely to require supplemental oxygen compared with NH white (aOR = 0.5 [95% CI: 0.4–0.8]) and Hispanic or Latino children (aOR = 0.6 [95% CI: 0.4–0.9]). Relative to 0- to 2-month-old children, 6- to 11-month-old (aOR = 1.7 [95% CI: 1.1–2.7]) and 24- to 59-month-old children (aOR = 1.7 [95% CI: 1.1–2.8]) were more likely to require supplemental oxygen; however, the difference for 24- to 59-month-old children did not remain statistically significant when including having any comorbid condition in the model. Remaining comparisons revealed no associations with supplemental oxygen receipt or ICU admission for day care and/or school attendance, other children living in the same household, household members who smoked, or history of breastfeeding.

Rates of RSV-Associated Hospitalizations

More than three-quarters (78.4%) of children who were RSV-positive

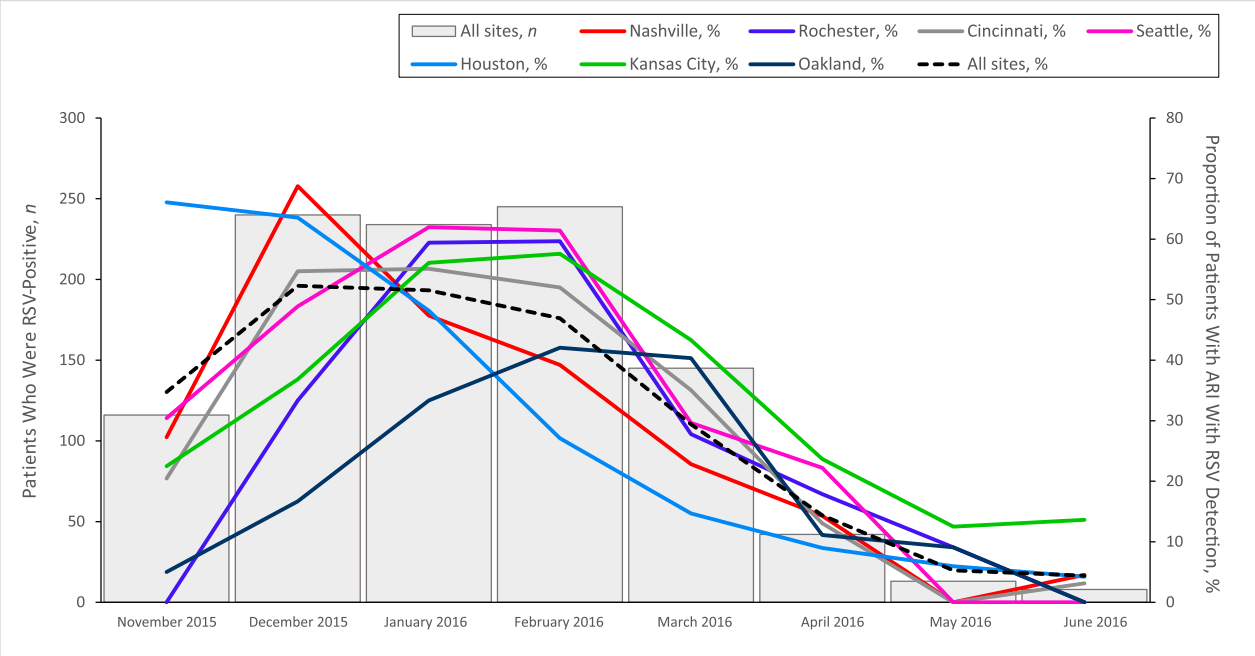

FIGURE 2
RSV-associated hospitalized children <5 years of age by enrollment date and site.

resided in the counties used to calculate hospitalization rate estimates. The rate of RSV-associated hospitalizations across all sites was 2.9 (95% CI: 2.8–3.1) per 1000 children <5 years old and 6.3 (95% CI: 5.9–6.7) per 1000 children <24 months old (Supplemental Table 8, Table 4). Younger infants had the highest rates of hospitalization, with 14.7 (95% CI: 13.6–15.9) hospitalized per 1000 children <6 months old and 18.9 (95% CI: 17.0–20.9) per 1000 children <2 months old. Individual site rates of RSV hospitalizations ranged from 1.8 to 6.5 per 1000 children <5 years old and 8.2 to 32.4 per 1000 children <6 months old (Supplemental Table 8).

Estimated rates of RSV-associated hospitalization among children <24 months old by chronological month of age were highest in 1-month-old infants (25.1 [95% CI: 21.1–29.3] per 1000). The next highest rates were in <1- and 2-month-old infants and decreased by subsequent months through 10 months of age (Table 4).

Among children <24 months old, the RSV-associated hospitalization rate for those with a reported preterm birth (9.6 [95% CI 8.1–11.1] per 1000 children) was higher than for term-born children (5.8 [95% CI: 5.4–6.3] per 1000). Further analyses stratified by gestational age yielded rates of 15.4 (95% CI: 7.3–24.3) per 1000 for those <29 WGA, 13.8 (95% CI: 8.1–20.8) per 1000 for 29 to 31 WGA, 11.3 (95% CI: 8.1–14.6) per 1000 for 32 to 34 WGA, and 7.4 (95% CI: 5.8–9.2) per 1000 for 35 to 36 WGA. Rates for gestational age groups <35 weeks were statistically significantly higher than those for the ≥37 WGA group (Supplemental Table 9).

Among children <5 years old, the RSV-associated hospitalization rate was higher among male (3.3 [95% CI: 3.0–3.6] per 1000) than female (2.6 [95% CI: 2.3–2.9] per 1000) children. Similarly, higher rates were observed among Hispanic or Latino children (3.3 [95% CI: 3.0–3.7] per 1000) and NH African American children (3.4 [95% CI: 2.9–3.8] per 1000) compared with NH white children (2.5 [95% CI: 2.3–2.8] per 1000). The higher rate estimates for Hispanic or Latino and NH African American children relative to NH white children were also observed in the 6- to 11- and 24- to 59-month age groups (Supplemental Table 9).

DISCUSSION

RSV was associated with more than one-third of ARI hospitalizations among US children <5 years old during the 2015–2016 season of multicenter surveillance. An estimated 2.9 per 1000 children <5 years old were hospitalized with RSV, with the highest rates observed among the youngest infants (25.1 per 1000 infants 1 month old). Extrapolating to the US population, we estimate 58 000 (95% CI: 56 000–62 000) RSV-associated annual hospitalizations among children <5 years old, including 50 400 (87%; 95% CI: 47 000–53 000) in those <2 years

TABLE 1 Patient Demographics

Characteristic	RSV-Positive (n = 1043), n (%)[a]	RSV-Negative (n = 1926), n (%)[a]	P[b]
Sex			
Male	587 (56.3)	1140 (59.2)	.12
Female	456 (43.7)	786 (40.8)	—
Age, mo			
0–2	342 (32.8)	401 (20.8)	<.001
3–5	184 (17.6)	121 (6.3)	—
6–11	178 (17.1)	294 (15.3)	—
12–23	199 (19.1)	503 (26.1)	—
24–59	140 (13.4)	607 (31.5)	—
Ethnicity and/or race			
NH ethnicity	739 (70.9)	1307 (67.9)	.09[c]
White	438 (59.3)	622 (47.6)	<.001
African American	187 (25.3)	461 (35.3)	—
Other	114 (15.4)	222 (17.0)	—
Unknown or refused	0 (0.0)	2 (0.2)	—
Hispanic or Latino ethnicity	304 (29.1)	619 (32.1)	—
White	181 (59.5)	353 (57.0)	.81
African American	6 (2.0)	10 (1.6)	—
Other	88 (28.9)	187 (30.2)	—
Unknown or refused	29 (9.5)	69 (11.1)	—
Health insurance			
Public	623 (59.7)	1198 (62.2)	.03
Private	345 (33.1)	565 (29.3)	—
Both	25 (2.4)	79 (4.1)	—
None, self-pay	43 (4.1)	67 (3.5)	—
Unknown	7 (0.7)	17 (0.9)	—
Surveillance site			
Rochester	110 (38.9)	173 (61.1)	<.001
Cincinnati	151 (33.7)	297 (66.3)	—
Nashville	146 (37.5)	243 (62.5)	—
Kansas City	126 (37.4)	211 (62.6)	—
Houston	267 (33.4)	533 (66.6)	—
Seattle	138 (42.3)	188 (57.7)	—
Oakland	105 (27.2)	281 (72.8)	—

—, not applicable.

[a] Column percentages are presented for all variables except for surveillance site locations, for which row percentages are presented. Note that column percentages for race are nested within NH and Hispanic or Latino ethnicity totals, respectively.

[b] P values of χ^2 analyses for characteristics between hospitalized children with or without RSV infection.

[c] P value for comparison between children of Hispanic or Latino ethnicity and NH ethnicity.

old. Among children <2 years old, higher hospitalization rates were associated with preterm birth at <35 weeks' gestation. However, most hospitalized children who were RSV-positive had no history of prematurity or underlying medical condition, suggesting that otherwise healthy young children, in addition to children at high risk, could benefit from interventions against RSV.

RSV continues to be a major cause of hospitalized ARI among young children worldwide.[1–3,8,25,26] Although previous US estimates of RSV disease relied on administrative databases,[4–8] active prospective population-based surveillance generates more precise burden estimates.[1,2] Our rates are comparable to earlier US estimates from 3 of the same surveillance sites that employed similar methodology (Rochester, Nashville, and Cincinnati), which included an overall rate of 3.0 hospitalizations per 1000 children <5 years old in 2000–2004[1] and the highest rates by month of age also observed in the youngest infants in 2000–2005 (as high as 25.9 per 1000 children 1 month old).[2] Current study enrollment was similarly based on admission with ARI-related conditions and collection of nasal and throat swabs. However, the current study features 4 additional surveillance sites, making the current network more geographically representative of the United States. This and other differences (eg, current molecular diagnostics and one-year surveillance period) limit further direct comparisons to the previous studies. However, our data reveal the continued substantial burden of pediatric RSV infections in the United States.

A history of prematurity was another factor associated with higher rates of RSV-associated hospitalization, in addition to younger age. Among children <24 months old, hospitalization rates were higher among children born at <35 WGA compared with term-born children. However, because of the relatively low case numbers from one season of data, no conclusions could be made regarding differences among rates for gestational age groups <35 WGA. Point estimates for 29 to 31 WGA and 32 to 34 WGA were higher than previously reported, but conclusive comparisons were not possible given the relatively small case numbers in these groups.[2] In addition, although the proportion of children <2 years old who were RSV-positive with reported palivizumab administration (2%) was comparable to that in 2000–2005 (3%),[2] these data were obtained by unverified parental history, limiting further analyses.

In considering other characteristics previously associated with severe RSV disease, such as male sex, race, underlying medical conditions, and environmental factors (including exposure to smoking and contact with other children),[27–35] we found higher RSV-associated hospitalization rates among male children, NH African American children, and Hispanic or Latino children that were statistically significant but small in magnitude. Although higher rates of RSV hospitalization in ≥12-month-old

TABLE 2 Patient History and Clinical Characteristics

Characteristic	RSV-Positive (n = 1043)	RSV-Negative (n = 1926)	P[a]
Any comorbid condition,[b] *n* (%)	217 (20.8)	714 (37.1)	<.001
Chronic lung disease	117 (11.2)	455 (23.6)	<.001
Congenital heart disease	46 (4.4)	106 (5.5)	.20
Neurologic and/or neuromuscular disease	43 (4.1)	118 (6.1)	.02
Immunocompromised condition	13 (1.2)	60 (3.1)	.002
History of prematurity (<37 wk),[c] *n* (%)	162 (17.9)	300 (22.7)	.006
Received palivizumab,[c] *n* (%)	21 (2.3)	95 (7.2)	<.001
Comorbid condition or history of prematurity, *n* (%)	339 (32.5)	892 (46.3)	<.001
Other children in household, *n* (%)			
<5 y old	454 (43.5)	717 (37.2)	<.001
5–17 y old	537 (51.5)	1066 (55.3)	.04
No other children	260 (24.9)	495 (25.7)	.64
Any household member is a smoker, *n* (%)	260 (24.9)	487 (25.3)	.83
History of breastfeeding, *n* (%)			
Any duration	825 (79.1)	1506 (78.2)	.57
Duration			
Never	215 (20.6)	410 (21.3)	<.001
<1 mo	225 (21.6)	342 (17.8)	—
1–6 mo	466 (44.7)	766 (39.8)	—
≥7 mo	127 (12.2)	376 (19.5)	—
Not specified	7 (0.7)	22 (1.1)	—
Maternal education of high school or less, *n* (%)	613 (58.8)	1163 (60.4)	.39
Day care and/or school attendance, *n* (%)			
>4 h/wk	270 (25.9)	569 (29.5)	.03
Attendees			
<6 attendees	64 (6.1)	116 (6.0)	.004
6–12 attendees	152 (14.6)	276 (14.3)	—
>12 attendees	48 (4.6)	159 (8.3)	—
Unknown	6 (0.6)	18 (0.9)	—
Intervention received, *n* (%)			
Supplemental oxygen	718 (68.8)	968 (50.3)	<.001
ICU admission	182 (17.4)	256 (13.3)	.002
Mechanical ventilation	27 (2.6)	69 (3.6)	.14
Length of stay, median, d (range)	2 (<1–95)	2 (<1–107)	—
0–1 d, *n* (%)	272 (26.1)	775 (40.2)	<.001
2 d, *n* (%)	295 (28.3)	616 (32.0)	—
3–4 d, *n* (%)	295 (28.3)	323 (16.8)	—
≥5 d, *n* (%)	181 (17.4)	212 (11.0)	—
Deaths, *n* (%)	0 (0.0)	1 (0.1)	.46

—, not applicable

[a] P values of χ^2 analyses for characteristics between hospitalized children with or without RSV infection.

[b] Comorbid conditions included chronic pulmonary and/or airway, cardiac, gastrointestinal, kidney, endocrine, neurologic and/or neuromuscular, hematologic and/or oncologic, genetic and/or metabolic, or immunocompromised conditions.

[c] History of prematurity and palivizumab receipt information was reported for children aged <2 y; percentages calculated out of total RSV-associated hospitalized children by age group.

children have been previously observed among NH African American versus NH white children at 3 surveillance sites (Rochester, Nashville, and Cincinnati) over multiple years, analyses of Hispanic or Latino children were not possible in those studies because of low numbers.[30] The addition of 4 new surveillance sites raised the proportion of Hispanic or Latino children closer to that of the US population[19] and allowed for additional rate estimates by Hispanic or Latino ethnicity.

TABLE 3 RSV-Associated Hospitalized Children <2 Years of Age by Gestational Age and Age Group

Gestational Age at Birth	0–2 mo	3–5 mo	6–11 mo	12–23 mo	<24 mo
<29 wk, *n* (%)	0 (0)	2 (1)	6 (3)	11 (6)	19 (2)
29–31 wk, *n* (%)	2 (1)	3 (2)	8 (4)	5 (3)	18 (2)
32–34 wk, *n* (%)	14 (4)	16 (9)	11 (6)	9 (5)	50 (6)
35–36 wk, *n* (%)	34 (10)	18 (10)	12 (7)	6 (3)	70 (8)
≥37 wk, *n* (%)	288 (84)	144 (78)	141 (79)	164 (82)	737 (82)
Total,[a] *n*	342	184	178	199	903

[a] Includes 4 patients with an unknown history of prematurity and 5 patients with a history of prematurity with unknown gestational age.

Limitations of our study include that surveillance started on November 1, 2015, after RSV season had begun in certain regions (in late September to October) containing a number of our sites (Nashville, Cincinnati, Houston, and Rochester),[36] which would contribute to the underestimation of hospitalization rates, and covered one winter season, which precluded assessment of seasonal variation. In addition, surveillance was performed in major urban pediatric medical centers that may not fully represent other areas of the United States. Despite these limitations, our estimates rely on a sensitive surveillance platform optimized to capture pediatric RSV disease, which includes the use of a broad case definition that ensures the capture of RSV infections that present without fever, seen particularly among younger infants.[37] In addition, prospective testing using current molecular diagnostic techniques and specimen collection methods ensured sensitive detection not dependent on clinical testing that can vary by practitioner or institution and, in cases of bronchiolitis, is not recommended routinely.[38]

Our findings represent renewed surveillance efforts at geographically diverse study locations to characterize RSV burden in young US children. With new immunoprophylaxis, antiviral, and vaccine products in development,[10,11,39] continued surveillance is important to establish robust estimates of RSV burden so that the impact of future products can be assessed. In particular, stratification of infant rates by month of age should help inform planning for prevention measures such as

TABLE 4 Rates of Inpatient RSV Infection by Month of Age Among Children <24 Months of Age

Age, mo[a]	Rate per 1000	95% CI
<1	16.1	12.9–19.4
1	25.1	21.1–29.3
2	15.6	13.2–18.1
3	13.4	10.8–16.1
4	9.9	7.5–12.2
5	8.3	6.1–10.4
6	8.2	6.3–10.3
7	4.8	3.1–6.6
8	4.5	2.8–6.2
9	3.9	2.1–6.0
10	2.7	1.4–4.1
11	4.5	2.6–6.6
12	3.6	2.0–5.2
13	3.6	2.1–5.4
14	3.5	2.0–5.2
15	2.7	1.5–4.0
16	2.9	1.7–4.2
17	5.2	3.2–7.4
18	N/A	N/A
19	2.6	1.3–4.1
20	3.8	2.5–5.3
21	N/A	N/A
22	N/A	N/A
23	N/A	N/A
<24	6.3	5.9–6.7

N/A, estimates are not available because of relative SE >30%.

[a] Children were defined as being <1 mo old if the child had not yet reached 1 mo of age, 1 mo old if the child was between 1 and <2 mo old, etc.

vaccines and immune intervention strategies (eg, maternal vaccines and specifically targeted monoclonal antibodies) that target infants <6 months old.[9,11] An improved understanding of the epidemiology of RSV disease among young children should help prioritize these interventions in the context of overall public health strategies. Because most children hospitalized with RSV have no underlying medical conditions or history of prematurity, interventions against RSV used to broadly target all young infants are likely to result in the greatest impact.

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ABBREVIATIONS

aOR: adjusted odds ratio
ARI: acute respiratory illness
CDC: Centers for Disease Control and Prevention
CI: confidence interval
HPIV: human parainfluenza virus
NH: non-Hispanic or non-Latino
RSV: respiratory syncytial virus
WGA: weeks' gestational age

Dr Rha conceptualized and designed the study, designed data collection instruments, supervised data collection nationally, provided substantial contributions to analysis and interpretation of the data, drafted the initial manuscript, and critically reviewed and revised the manuscript; Dr Gerber conceptualized and designed the study, supervised data collection nationally, supervised data analyses and interpretation, and critically reviewed and revised the manuscript; Mr Curns made substantial contributions to the design of the study, supervised data collection nationally, led performance of analyses and interpretation of the data, and critically reviewed and revised the manuscript; Ms Lively provided substantial contributions to supervision of data collection nationally, helped perform data analyses, and critically reviewed and revised the manuscript; Dr Campbell provided substantial contributions to the conception and design of the study, the design of data collection instruments, and the interpretation of the data and critically reviewed and revised the manuscript; Drs Englund, Boom, Azimi, Weinberg, Staat, Selvarangan, and Halasa provided substantial contributions to conception and design of the study and design of data collection instruments, supervised data collection locally, provided substantial contributions to interpretation of the data, and critically reviewed and revised the manuscript for important intellectual content; Ms McNeal and Drs Klein, Harrison, Williams, Szilagyi, Singer, and Sahni provided substantial contributions to the supervision of local data collection and interpretation of data and critically reviewed and revised the manuscript for important intellectual content; Ms Figueroa-Downing provided substantial contributions to the design of the study and data collection instruments and supervision of data collection nationally, helped perform initial data analyses, and critically reviewed and revised the manuscript; Mr McDaniel helped supervise data collection nationally, performed initial data analyses, and critically reviewed and revised the manuscript; Ms Prill helped supervise data collection nationally and critically reviewed and revised the manuscript; Mr Whitaker contributed to the design of the study, provided substantial contributions to the collection and interpretation of laboratory data, and critically reviewed and revised the manuscript for important intellectual content; Dr Payne provided substantial contributions to the conception and design of the study, helped supervise data collection nationally, and critically reviewed and revised the manuscript; Dr Langley provided substantial contributions to study design and interpretation of the data and critically reviewed and revised the manuscript; Drs Stewart, Schuster, Pahud, and Weddle helped supervise local data collection and critically reviewed and revised the manuscript; Drs Piedra, Munoz, and Avadhanula provided substantial contributions to local data collection and interpretation of data and critically reviewed and revised the manuscript for important intellectual content; and all authors approved the final manuscript as submitted and agree to be accountable for all

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Address correspondence to Brian Rha, MD, MSPH, Division of Viral Diseases, Centers for Disease Control and Prevention, 1600 Clifton Rd NE, Mailstop H24-5, Atlanta, GA 30329. E-mail: wif8@cdc.gov

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REFERENCES

1. Hall CB, Weinberg GA, Iwane MK, et al. The burden of respiratory syncytial virus infection in young children. *N Engl J Med*. 2009;360(6):588–598
2. Hall CB, Weinberg GA, Blumkin AK, et al. Respiratory syncytial virus-associated hospitalizations among children less than 24 months of age. *Pediatrics*. 2013; 132(2). Available at: www.pediatrics.org/cgi/content/full/132/2/e341
3. Iwane MK, Edwards KM, Szilagyi PG, et al; New Vaccine Surveillance Network. Population-based surveillance for hospitalizations associated with respiratory syncytial virus, influenza virus, and parainfluenza viruses among young children. *Pediatrics*. 2004;113(6): 1758–1764
4. Shay DK, Holman RC, Newman RD, Liu LL, Stout JW, Anderson LJ. Bronchiolitis-associated hospitalizations among US children, 1980–1996. *JAMA*. 1999; 282(15):1440–1446
5. Leader S, Kohlhase K. Recent trends in severe respiratory syncytial virus (RSV) among US infants, 1997 to 2000. *J Pediatr*. 2003;143(suppl 5): S127–S132
6. Zhou H, Thompson WW, Viboud CG, et al. Hospitalizations associated with influenza and respiratory syncytial virus in the United States, 1993–2008. *Clin Infect Dis*. 2012;54(10):1427–1436
7. Matias G, Taylor R, Haguinet F, Schuck-Paim C, Lustig R, Shinde V. Estimates of hospitalization attributable to influenza and RSV in the US during 1997–2009, by age and risk status. *BMC Public Health*. 2017;17(1):271
8. Stockman LJ, Curns AT, Anderson LJ, Fischer-Langley G. Respiratory syncytial virus-associated hospitalizations among infants and young children in the United States, 1997–2006. *Pediatr Infect Dis J*. 2012;31(1):5–9
9. American Academy of Pediatrics Committee on Infectious Diseases; American Academy of Pediatrics Bronchiolitis Guidelines Committee. Updated guidance for palivizumab prophylaxis among infants and young children at increased risk of hospitalization for respiratory syncytial virus infection [published correction appears in *Pediatrics*. 2014;134(6): 1221]. *Pediatrics*. 2014;134(2):415–420
10. PATH. RSV vaccine and mAb snapshot. 2019. Available at: https://path.org/resources/rsv-vaccine-and-mab-snapshot/. Accessed November 7, 2019
11. Mazur NI, Higgins D, Nunes MC, et al; Respiratory Syncytial Virus Network (ReSViNET) Foundation. The respiratory syncytial virus vaccine landscape: lessons from the graveyard and promising candidates [published correction appears in *Lancet Infect Dis*. 2018;18(9):941]. *Lancet Infect Dis*. 2018; 18(10):e295–e311
12. Gonsalves S, Mahony J, Rao A, Dunbar S, Juretschko S. Multiplexed detection and identification of respiratory pathogens using the NxTAG® respiratory pathogen panel. *Methods*. 2019;158: 61–68
13. Poritz MA, Blaschke AJ, Byington CL, et al. FilmArray, an automated nested multiplex PCR system for multi-pathogen detection: development and application to respiratory tract infection [published correction appears in *PLoS One*. 2011;6(11):10.1371/annotation/468cfdcd-184c-42f7-a1d0-3b72a2f6a558]. *PLoS One*. 2011;6(10): e26047
14. Kodani M, Yang G, Conklin LM, et al. Application of TaqMan low-density arrays for simultaneous detection of multiple respiratory pathogens. *J Clin Microbiol*. 2011;49(6):2175–2182
15. Weinberg GA, Schnabel KC, Erdman DD, et al. Field evaluation of TaqMan Array Card (TAC) for the simultaneous detection of multiple respiratory

viruses in children with acute respiratory infection. *J Clin Virol*. 2013; 57(3):254–260

16. Avadhanula V, Chemaly RF, Shah DP, et al. Infection with novel respiratory syncytial virus genotype Ontario (ON1) in adult hematopoietic cell transplant recipients, Texas, 2011–2013. *J Infect Dis*. 2015;211(4):582–589
17. Beckham JD, Cadena A, Lin J, et al. Respiratory viral infections in patients with chronic, obstructive pulmonary disease. *J Infect*. 2005;50(4):322–330
18. Klemenc J, Asad Ali S, Johnson M, et al. Real-time reverse transcriptase PCR assay for improved detection of human metapneumovirus. *J Clin Virol*. 2012; 54(4):371–375
19. National Center for Health Statistics; Centers for Disease Control and Prevention. National vital statistics system: bridged-race population estimates - data files and documentation. Available at: https://www.cdc.gov/nchs/nvss/bridged_race/data_documentation.htm#vintage2016. Accessed March 4, 2019.
20. Martin JA, Hamilton BE, Osterman MJK, Curtin SC, Matthews TJ. Births: final data for 2013. *Natl Vital Stat Rep*. 2015; 64(1):1–65
21. Hamilton BE, Martin JA, Osterman MJK, Curtin SC, Matthews TJ. Births: final data for 2014. *Natl Vital Stat Rep*. 2015; 64(12):1–64
22. Martin JA, Hamilton BE, Osterman MJK, Driscoll AK, Mathews TJ. Births: final data for 2015. *Natl Vital Stat Rep*. 2017; 66(1):1–70
23. Martin JA, Hamilton BE, Osterman MJK, Driscoll AK, Drake P. Births: final data for 2016. *Natl Vital Stat Rep*. 2018;67(1): 1–55
24. Efron B, Tibshirani RJ. *An Introduction to the Bootstrap*. Boca Raton, FL: CRC Press LLC; 1998
25. Jain S, Williams DJ, Arnold SR, et al; CDC EPIC Study Team. Community-acquired pneumonia requiring hospitalization among U.S. children. *N Engl J Med*. 2015;372(9):835–845
26. Shi T, McAllister DA, O'Brien KL, et al; RSV Global Epidemiology Network. Global, regional, and national disease burden estimates of acute lower respiratory infections due to respiratory syncytial virus in young children in 2015: a systematic review and modelling study. *Lancet*. 2017; 390(10098):946–958
27. Simoes EAF. Environmental and demographic risk factors for respiratory syncytial virus lower respiratory tract disease. *J Pediatr*. 2003;143(suppl 5):S118–S126
28. Langley GF, Anderson LJ. Epidemiology and prevention of respiratory syncytial virus infections among infants and young children. *Pediatr Infect Dis J*. 2011;30(6):510–517
29. Bont L, Checchia PA, Fauroux B, et al. Defining the epidemiology and burden of severe respiratory syncytial virus infection among infants and children in Western countries. *Infect Dis Ther*. 2016; 5(3):271–298
30. Iwane MK, Chaves SS, Szilagyi PG, et al. Disparities between black and white children in hospitalizations associated with acute respiratory illness and laboratory-confirmed influenza and respiratory syncytial virus in 3 US counties—2002–2009. *Am J Epidemiol*. 2013;177(7):656–665
31. Sangaré L, Curtis MP, Ahmad S. Hospitalization for respiratory syncytial virus among California infants: disparities related to race, insurance, and geography. *J Pediatr*. 2006;149(3): 373–377
32. Doucette A, Jiang X, Fryzek J, Coalson J, McLaurin K, Ambrose CS. Trends in respiratory syncytial virus and bronchiolitis hospitalization rates in high-risk infants in a United States nationally representative database, 1997-2012. *PLoS One*. 2016;11(4): e0152208
33. Bradley JP, Bacharier LB, Bonfiglio J, et al. Severity of respiratory syncytial virus bronchiolitis is affected by cigarette smoke exposure and atopy. *Pediatrics*. 2005;115(1). Available at: www.pediatrics.org/cgi/content/full/115/1/e7
34. Law BJ, Langley JM, Allen U, et al. The Pediatric Investigators Collaborative Network on Infections in Canada study of predictors of hospitalization for respiratory syncytial virus infection for infants born at 33 through 35 completed weeks of gestation. *Pediatr Infect Dis J*. 2004; 23(9):806–814
35. Nielsen HE, Siersma V, Andersen S, et al. Respiratory syncytial virus infection--risk factors for hospital admission: a case-control study. *Acta Paediatr*. 2003;92(11):1314–1321
36. Rose EB, Wheatley A, Langley G, Gerber S, Haynes A. Respiratory syncytial virus seasonality - United States, 2014–2017. *MMWR Morb Mortal Wkly Rep*. 2018; 67(2):71–76
37. Rha B, Dahl RM, Moyes J, et al. Performance of surveillance case definitions in detecting respiratory syncytial virus infection among young children hospitalized with severe respiratory illness-South Africa, 2009–2014. *J Pediatric Infect Dis Soc*. 2019;8(4):325–333
38. Ralston SL, Lieberthal AS, Meissner HC, et al. Clinical practice guideline: the diagnosis, management, and prevention of bronchiolitis [published correction appears in *Pediatrics*. 2015;136(4):782]. *Pediatrics*. 2014;134(5). Available at: www.pediatrics.org/cgi/content/full/134/5/e1474
39. Mazur NI, Martinón-Torres F, Baraldi E, et al; Respiratory Syncytial Virus Network (ReSViNET). Lower respiratory tract infection caused by respiratory syncytial virus: current management and new therapeutics. *Lancet Respir Med*. 2015;3(11):888–900