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SUPPLEMENT ARTICLE

# Medically Attended Illness due to Respiratory Syncytial Virus Infection Among Infants Born in the United States Between 2016 and 2020

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***Background.*** Respiratory syncytial virus (RSV) is a leading cause of infant hospitalization in the United States. Preterm infants and those with select comorbidities are at highest risk of RSV-related complications. However, morbidity due to RSV infection is not confined to high-risk infants. We estimated the burden of medically attended (MA) RSV-associated lower respiratory tract infection (LRTI) among infants in the United States.

***Methods.*** We analyzed commercial (MarketScan Commercial [MSC], Optum Clinformatics [OC]), and Medicaid (MarketScan Medicaid [MSM]) insurance claims data for infants born between April 2016 and February 2020. Using both specific and sensitive definitions of MA RSV LRTI, we estimated the burden of MA RSV LRTI during infants' first RSV season, stratified by gestational age, comorbidity status, and highest level of medical care associated with the MA RSV LRTI diagnosis.

***Results.*** According to the specific definition 75.0% (MSC), 78.6% (MSM), and 79.6% (OC) of MA RSV LRTI events during infants' first RSV season occurred among term infants without known comorbidities.

***Conclusions.*** Term infants without known comorbidities account for up to 80% of the MA RSV LRTI burden in the United States during infants' first RSV season. Future prevention efforts should consider all infants.

**Keywords.** respiratory syncytial virus; infants; burden.

Respiratory syncytial virus (RSV) is a major cause of morbidity and mortality among infants globally [1] and a leading cause of infant hospitalization in the United States [2–4]. While infants born preterm and/or those with select comorbidities are at higher risk of severe complications due to RSV [2–7], studies have indicated that term infants without known comorbidities account for over 70% of RSV-related hospitalizations [3, 8, 9]. Current guidelines recommend that infants with certain comorbidities receive the prophylactic antibody palivizumab [10, 11]; however, the overall RSV burden among all infants remains high [6], and no vaccine is yet available for the prevention of RSV infection. Immunization products such as vaccines and monoclonal antibodies are under development. Targeting future prevention efforts optimally will rely not only on identifying specific infants at particularly high risk of hospitalization but also on addressing the overall public health burden and severity of RSV-related disease among all infants and across different health care settings [9, 12].

In this study, we estimated the burden of medically attended (MA) lower respiratory tract infection (LRTI) due to RSV among infants in the United States during their first RSV season. Our primary objectives were (1) to quantify the MA RSV LRTI burden attributable to comorbidity groups defined by gestational age and the presence of underlying medical conditions, and (2) to identify the highest level of medical care during MA RSV LRTI episodes. Our secondary objective was to estimate rates of MA RSV LRTI diagnosis specific to comorbidity groups defined by the presence or absence of comorbidities that predispose infants to severe RSV-related complications. We generated and compared results from 2 commercial insurance claims data sets (MarketScan Commercial [MSC] and Optum Clinformatics [OC]) and the MarketScan Medicaid (MSM) data set. These 3 data sets capture different cross-sections of the infant population in the United States, particularly Medicaid, which contains infants of potentially lower socioeconomic status compared to the commercial data sets.

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## METHODS

### Birth Cohorts

We used deidentified data on commercial insurance and Medicaid claims to build 3 separate retrospective birth cohorts of infants born between 1 April 2016 and 29 February 2020. The 3 cohorts represent different subpopulations of infants in the United States. Commercial health claims data came from the MSC Claims and Encounters and OC data sets, while Medicaid data came from the MSM Multi-State Database. MSC contains data on fee-for-service and managed care health plans, including cost, use, and outcomes from both inpatient and outpatient settings. MSM contains data on Medicaid enrollees from a geographically dispersed set of states, including inpatient and outpatient services and outcomes. OC contains administrative health claims for members of a large national managed care company affiliated with Optum, including data on inpatient and outpatient diagnoses, procedures, and outcomes. As our study involved only secondary analysis of fully deidentified data, the work does not constitute human subjects research and is not subject to institutional review board review.

We included infants in each birth cohort if they could be linked to a claim indicating live discharge from a birth hospitalization. We linked infants to their Census division at birth, using date of admission as a proxy for birth date in the Optum data. Census divisions group states into discrete geographical units [13]. To account for differential RSV transmission dynamics by geographic area, each infant's first RSV season was assigned onset and offset dates specific to Census division. The division-specific dates were determined by the Centers for Disease Control and Prevention [14]. In OC, we linked infants to their birth mothers to retrieve demographic information or codes related to gestational age at delivery or pregnancy term, although we did not exclude infants who could not be linked to mothers' delivery records.

### Respiratory Syncytial Virus

Given limited availability of laboratory data and the absence of routine RSV testing, we defined MA RSV LRTI using both a specific and a sensitive RSV definition. The specific definition consisted of International Classification of Diseases-Tenth Revision-Clinical Modification (ICD-10-CM) diagnosis codes that explicitly named RSV (B974, J121, J205, and J210). In the case of code B974, diagnoses that occurred during an emergency department or outpatient visit must also have been accompanied by another respiratory diagnosis within 5 days before or after the date of B974. The sensitive definition included all codes in the specific definition, plus 2 codes for unspecified bronchiolitis (J218 and J219). We consider estimates using the specific definition to represent a lower bound on the burden of MA RSV LRTI among infants, and the sensitive definition an upper bound. To align analyses across data sets, we considered diagnoses based on the maximum number of available diagnosis positions listed in MarketScan data: qualifying codes must have appeared within the first 4 diagnosis positions when listed during an outpatient or emergency department visit and within the first 15 diagnosis positions when listed during an inpatient stay. Complete ICD-10-CM code lists are presented in Supplementary Table 6.

Using these definitions, we identified MA RSV LRTI events and recorded the highest level of medical care associated with each as outpatient (lowest), emergency department, or inpatient (highest), using place of service codes recorded in claims (Supplementary Table 9).

We identified MA RSV LRTI episodes in the specific analysis as follows:

1. For each infant, identify an MA RSV LRTI diagnosis that meets the specific definition: the index diagnosis for a given episode.
2. Identify all RSV-related diagnoses (meeting the sensitive definition) occurring within 7 days following the index diagnosis.
3. Record the highest level of medical care among these RSV diagnoses.

In the sensitive analysis, we followed the same procedure but allowed the index diagnosis that triggered an MA RSV LRTI episode to match the sensitive outcome definition. For all analyses, we defined the outcome as the highest level of medical care during the first MA RSV LRTI diagnosis (episode) that occurred during an infant's first RSV season, excluding MA RSV LRTI diagnoses recorded prior to the season's onset.

### Comorbidity Groups

We assigned infants to comorbidity groups defined by maternal gestational age at delivery and the presence of comorbidities. Infants were considered to have a given comorbidity if the diagnosis predated their first in-season MA RSV LRTI diagnosis or, among those without an MA RSV LRTI diagnosis, at any point prior to censoring. Comorbidity group A consisted of term infants without known comorbidities. We considered infants with no ICD-10-CM code for gestational age but with diagnosis-related group codes 789, 793, 794, 795, or missing to be term infants, assuming the lack of explicit coding for preterm birth indicated the condition was absent. A similar method was found to have a positive predictive value of 91% and a negative predictive value of 83% for identifying term deliveries, validated against birth certificates [15]. Comorbidity group B consisted of preterm infants with or without chronic lung disease (CLD) or hemodynamically significant congenital heart disease (HS-CHD). Comorbidity group C consisted of preterm infants without CLD or HS-CHD and term infants with other

comorbid conditions but without HS-CHD. Groups B and C we refer to, respectively, as "palivizumab eligible" and "other comorbidities" [10, 11]. The characteristics of group B, however, only approximate palivizumab eligibility due to the unavoidable use of code-based proxies in insurance claims data (leading to potential misclassification of palivizumab eligibility). Group B contains 4 subgroups: B1, all preterm infants <29 weeks' gestational age (wGA); B2, 29–31 wGA, with CLD; B3, 29+ wGA, with HS-CHD; and B4, preterm, unknown GA, with CLD, HS-CHD, or both. Group C also contains 4 subgroups: C1, 29–31 wGA, with neither CLD nor HS-CHD; C2, 32–36 wGA, without HS-CHD; C3, preterm, unknown GA, with neither CLD nor HS-CHD; and C4, 37+ wGA with comorbid conditions but no HS-CHD. While no overlap existed between comorbidity groups B and C, subgroups within B and C were not necessarily mutually exclusive. See Supplementary Tables 2, 7, and 8 and the lattermost's accompanying CSV file for details regarding comorbidity group assignment.

### Variables

We described the study population by dataset using the variables discussed below, all of which we also used in the estimation of inverse probability of censoring weights (IPCW) described in section "Statistical Analysis." All variables were treated as categorical.

We recorded calendar birth month (January through December) and birth year (2016–2020). Sex at birth was recorded as male or female, although we retained a small number of infants with unknown sex. Census division at birth was assessed in commercial data and included New England, Mid Atlantic, East North Central, West North Central, South Atlantic, East South Central, West South Central, Mountain, Pacific, or Other. MSM data did not include information on Census division. Low birth weight was assessed as a binary measure of having an ICD-10-CM code that indicated low birth weight (codes P700–P703 and P0710–P0718) or not. Gestational age was recorded as <29 weeks, 29–31 weeks, 32–36 weeks, full term (>36 weeks), preterm with unknown gestational age, and unknown gestational age (assumed to be full-term unless accompanied by a diagnosis-related group code identifying a preterm birth). Insurance plan type was recorded as comprehensive/indemnity, exclusive provider organization/preferred provider organization, point of service (with or without capitation), health maintenance organization, consumer-driven health plan/high-deductible health plan, or missing/unknown. For each RSV definition, we also created a binary indicator for the presence of an MA RSV LRTI episode occurring prior to an infant's first RSV season (preseason RSV). The presence of comorbid conditions other than CLD or HS-CHD was assessed as a binary indicator, as were CLD and HS-CHD. Supplementary Table 8 (and its accompanying CSV file) present qualifying ICD-10-CM codes for each of these variables.

### Statistical Analysis

#### *Follow-Up*

We identified infants' first MA RSV LRTI episode beginning with each subject's date of discharge from their birth hospitalization or the Census division-specific onset date of their first RSV season, whichever occurred later. Infants were censored at the first of loss to follow-up due to disenrollment from insurance, occurrence of an MA RSV LRTI diagnosis, or the last day of their first RSV season. We did not exclude or censor infants who may have died during follow-up, under the assumption that accounting for the small number of deaths in this age group would negligibly affect our outcome estimates.

#### *Inverse Probability of Censoring Weights*

To account for potentially informative loss to follow-up due to disenrollment, we calculated stabilized inverse probability of censoring weights (IPCW) in each data set as a function of variables (or proxies of variables) we assumed might affect both loss to follow-up and MA RSV LRTI diagnosis [16–18]. We selected these variables based primarily on prior knowledge and assumption. Weight numerators were estimated as the probability of an infant's being observed through the end of their first RSV season, conditional on their comorbidity group. Weight denominators were estimated as the probability of an infant's being followed through the end of their first RSV season, conditional on comorbidity group and all covariates discussed in the "Variables" section (see Supplemental Methods; Supplementary Tables 3 and 4; and Supplementary Figure 2 and its accompanying CSV files for more information). We used penalized logistic regression models implemented by the *glmnet* package in R to model the weight denominators, choosing penalized methods to account for a larger number of variables and interaction terms than might have been possible had we used standard logistic regression [19, 20]. We also allowed for the following potential interactions: birth month by birth year, birth month by Census division (in commercial data only), birth month by comorbidity group, birth month by insurance plan type, and sex by comorbidity group. We selected the level of penalization in these models separately within each data set using 10-fold cross-validation [19].

#### *Outcomes*

Within the analytic sample from each data set, we characterized the overall burden of MA RSV LRTI by estimating outcome rates of MA RSV LRTI per 10 000 infants and stratified estimates by both comorbidity group and the highest level of medical care during the MA RSV LRTI episodes. We calculated overall outcome rates by dividing the weighted number of MA RSV LRTI diagnoses in each cell by the sum of IPCWs

among individuals in the analytic sample and then multiplying the result by 10 000 to get the final outcome rate. We estimated weighted comorbidity group-specific MA RSV LRTI outcome rates by dividing the weighted number of MA RSV LRTI diagnoses in each cell by the sum of IPCWs among individuals within the corresponding comorbidity group and then multiplying the result by 10 000 to get the final comorbidity group-specific rate. We used the *survey* package in R to calculate weighted point estimates and estimate 95% confidence limits using robust standard errors [21].

Using the weighted estimates described above, we calculated the cell proportion of MA RSV LRTI episodes (cell rate/overall rate) for each combination of comorbidity group and highest level of care. Finally, we used these cell proportions to estimate the proportion of MA RSV LRTI outcomes attributable to each comorbidity group.

## RESULTS

### Sample Characteristics

In the MSC data, we identified 644 116 infants linkable to a birth hospitalization during the study period. Of these, 561 317 (87.1%) were observed through the end of their first RSV season, while 82 799 (12.9%) were censored prior to the end of their first RSV season. In the MSM data, we identified 1 025 286 infants, 974 057 (95.0%) of whom were observed through the end of their first RSV season, while 51 229 (5.0%) were censored. In the OC data, we identified 460 426 infants, 296 548 (64.4%) of whom were observed through the end of their first RSV season, while 163 878 (35.6%) were censored (Table 1). These numbers refer to analyses under the sensitive MA RSV LRTI definition. See Supplementary Table 1 for the same quantities under the specific definition.

Qualitatively, measured sources of potentially informative censoring were similar across data sets, as indicated by standardized mean differences >0.1: birth month, birth year, Census division (commercial only), and insurance plan type (Table 1 and Supplementary Table 1). The IPCW estimated in all 3 data sets appeared to be well-behaved, with no evidence of extreme weights (Supplementary Table 4) [22]. All estimates presented in the "Results" section are weighted. Supplementary Table 2 depicts crude estimates of burden, while Supplementary Figure 3 compares the weighted complete case, unweighted complete case, and crude estimates of MA RSV LRTI burden.

### Rates of MA RSV LRTI, Overall

#### *Specific Definition*

Under the specific definition, the overall rates of MA RSV LRTI estimated in the MSC, MSM, and OC data sets were 502, 732, and 494 per 10 000 infants during their first RSV season (Table 2 and Figure 1). In the commercial data sets, outpatient diagnoses accounted for the majority of MA RSV LRTI diagnoses, while in the Medicaid data set, the outpatient setting accounted for just under half of MA RSV LRTI diagnoses, with increased representation of the emergency room (32%, compared to approximately 20% in commercial claims; Table 3).

#### *Sensitive Definition*

Under the sensitive definition, the overall rates calculated in the MSC, MSM, and OC data sets were 2–3 times higher, estimated at 1391, 1833, and 1252 per 10 000 infants (Table 2 and Figure 1). Relative to the specific definition, using the sensitive definition increased the proportion of MA RSV LRTI diagnoses assigned to the outpatient and inpatient settings across all data sets, decreased the proportion assigned to the emergency room in the MSC and OC data sets, and increased the proportion assigned to the emergency room in the MSM data set (Table 3).

### Rates of MA RSV LRTI, by Comorbidity Group

#### *Specific Definition*

Under the specific definition, comorbidity group-specific rates of having an outpatient MA RSV LRTI diagnosis were similar across the 3 comorbidity groups within each data set, although outpatient diagnoses among group A infants tended to be slightly lower compared to groups B and C (Table 4). Group B infants were the most likely to have an MA RSV LRTI diagnosis requiring inpatient admission, while group A infants had substantially lower rates of inpatient MA RSV LRTI compared to infants in groups B and C. In the MSC data, the overall rates of MA RSV LRTI were 472, 675, and 610 per 10 000 infants in groups A, B, and C, respectively. In the MSM data, these rates were 696, 909, and 903 per 10 000 infants, and in the OC data 472, 616, and 601 per 10 000 infants (Table 4).

#### *Sensitive Definition*

The findings under the specific MA RSV LRTI definition held qualitatively when using the sensitive definition. In the MSC data, the group-specific rates increased to 1315, 1974, and 1638 per 10 000 infants in groups A, B, and C, respectively. In the MSM data, these rates were 1736, 2574, and 2230 per 10 000 infants, and in the OC data they were 1203, 1552, and 1485 per 10 000 infants (Table 4).

### Share of Disease Burden, by Comorbidity Group

While infants in comorbidity group B were more likely to experience an inpatient MA RSV LRTI, the burden of MA RSV LRTI at all levels of care was primarily attributable to healthy term infants in comorbidity group A (Figure 1).

#### *Specific Definition*

Under the specific definition, comorbidity group A infants accounted for 75.0%, 78.6%, and 79.6% of MA RSV LRTI diagnoses in the MSC, MSM, and OC data sets, respectively. In

**Table 1. Characteristics of Infants Born Between 1 April 2016 and 29 February 2020 in the MarketScan Commercial, MarketScan Medicaid, and Optum Clinformatics Data Sets; Sensitive MA RSV LRTI analysis[a]**

| | MarketScan Commercial (n = 644 116) | | | | | MarketScan Medicaid (n = 1 025 286) | | | | | Optum Clinformatics (n = 460 426) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | LTFU (n = 82 799) | | Not LTFU (n = 561 317) | | | LTFU (n = 51 229) | | Not LTFU (n = 974 057) | | | LTFU (n = 163 878) | | Not LTFU (n = 296 548) | | |
| Variable | No. | % | No. | % | SMD[b] | No. | % | No. | % | SMD | No. | % | No. | % | SMD |
| Birth month | | | | | **0.530** | | | | | **0.644** | | | | | **0.411** |
| January | 2412 | 2.9 | 47 974 | 8.5 | | 1001 | 2.0 | 87 173 | 8.9 | | 9204 | 5.6 | 27 546 | 9.3 | |
| February | 1704 | 2.1 | 44 525 | 7.9 | | 581 | 1.1 | 75 600 | 7.8 | | 7778 | 4.7 | 26 416 | 8.9 | |
| March | 1437 | 1.7 | 39 569 | 7.0 | | 419 | 0.8 | 63 892 | 6.6 | | 4867 | 3.0 | 24 476 | 8.3 | |
| April | 4837 | 5.8 | 51 480 | 9.2 | | 2180 | 4.3 | 80 681 | 8.3 | | 8794 | 5.4 | 27 108 | 9.1 | |
| May | 10 469 | 12.6 | 49 104 | 8.7 | | 6395 | 12.5 | 82 332 | 8.5 | | 17 707 | 10.8 | 22 557 | 7.6 | |
| June | 10 447 | 12.6 | 48 541 | 8.6 | | 6448 | 12.6 | 82 550 | 8.5 | | 18 176 | 11.1 | 22 489 | 7.6 | |
| July | 10 131 | 12.2 | 50 400 | 9.0 | | 6310 | 12.3 | 87 397 | 9.0 | | 17 912 | 10.9 | 23 770 | 8.0 | |
| August | 10 125 | 12.2 | 51 695 | 9.2 | | 6545 | 12.8 | 90 892 | 9.3 | | 18 398 | 11.2 | 24 880 | 8.4 | |
| September | 9138 | 11.0 | 48 562 | 8.7 | | 5822 | 11.4 | 86 329 | 8.9 | | 16 936 | 10.3 | 24 301 | 8.2 | |
| October | 8583 | 10.4 | 47 702 | 8.5 | | 5552 | 10.8 | 84 443 | 8.7 | | 15 763 | 9.6 | 25 057 | 8.4 | |
| November | 7399 | 8.9 | 43 697 | 7.8 | | 5190 | 10.1 | 79 925 | 8.2 | | 14 582 | 8.9 | 23 772 | 8.0 | |
| December | 6117 | 7.4 | 38 068 | 6.8 | | 4786 | 9.3 | 72 843 | 7.5 | | 13 761 | 8.4 | 24 176 | 8.2 | |
| Birth year | | | | | **0.365** | | | | | **0.957** | | | | | **0.188** |
| 2016 | 25 711 | 31.1 | 115 828 | 20.6 | | 6356 | 12.4 | 212 778 | 21.8 | | 40 065 | 24.4 | 52 837 | 17.8 | |
| 2017 | 22 982 | 27.8 | 143 873 | 25.6 | | 34 810 | 67.9 | 253 765 | 26.1 | | 41 910 | 25.6 | 78 240 | 26.4 | |
| 2018 | 19 495 | 23.5 | 139 940 | 24.9 | | 5734 | 11.2 | 231 295 | 23.7 | | 39 576 | 24.1 | 77 770 | 26.2 | |
| 2019 | 14 373 | 17.4 | 141 784 | 25.3 | | 4267 | 8.3 | 239 536 | 24.6 | | 38 328 | 23.4 | 74 814 | 25.2 | |
| 2020 | 238 | 0.3 | 19 892 | 3.5 | | 62 | 0.1 | 36 683 | 3.8 | | 3999 | 2.4 | 12 887 | 4.3 | |
| Sex | | | | | 0.013 | | | | | 0.036 | | | | | 0.024 |
| Female | 40 615 | 49.1 | 271 704 | 48.4 | | 24 933 | 48.7 | 475 696 | 48.8 | | 80 005 | 48.8 | 143 906 | 48.5 | |
| Male | 42 184 | 50.9 | 289 613 | 51.6 | | 26 296 | 51.3 | 498 361 | 51.2 | | 83 770 | 51.1 | 152 592 | 51.5 | |
| Unknown | … | … | … | … | | 0 | 0.0 | 621 | 0.1 | | 103 | 0.1 | 50 | 0.0 | |
| Census division[c] | | | | | **0.217** | | | | | | | | | | **0.191** |
| New England | 3130 | 3.8 | 22 655 | 4.0 | | … | … | … | … | | 3293 | 2.0 | 7917 | 2.7 | |
| Mid Atlantic | 13 527 | 16.3 | 89 987 | 16.0 | | … | … | … | … | | 11 071 | 6.8 | 24 296 | 8.2 | |
| East North Central | 11 999 | 14.5 | 104 040 | 18.5 | | … | … | … | … | | 23 095 | 14.1 | 45 778 | 15.4 | |
| West North Central | 4543 | 5.5 | 42 714 | 7.6 | | … | … | … | … | | 14 641 | 8.9 | 37 735 | 12.7 | |
| South Atlantic | 17 704 | 21.4 | 113 015 | 20.1 | | … | … | … | … | | 38 166 | 23.3 | 59 400 | 20.0 | |
| East South Central | 2790 | 3.4 | 28 217 | 5.0 | | … | … | … | … | | 7295 | 4.5 | 9925 | 3.3 | |
| West South Central | 13 383 | 16.2 | 71 378 | 12.7 | | … | … | … | … | | 32 090 | 19.6 | 47 850 | 16.1 | |
| Mountain | 6916 | 8.4 | 43 151 | 7.7 | | … | … | … | … | | 17 973 | 11.0 | 31 946 | 10.8 | |
| Pacific | 8379 | 10.1 | 40 348 | 7.2 | | … | … | … | … | | 15 540 | 9.5 | 29 297 | 9.9 | |
| Other/unknown | 428 | 0.5 | 5812 | 1.0 | | … | … | … | … | | 714 | 0.4 | 2404 | 0.8 | |
| Comorbidity group | | | | | | | | | | | | | | | 0.033 |
| A: 37+ term infants, otherwise healthy | 68 079 | 82.2 | 456 547 | 81.3 | 0.023 | 41 563 | 81.1 | 797 156 | 81.8 | 0.018 | 138 322 | 84.4 | 247 127 | 83.3 | |
| B: Palivizumab-eligible | 1984 | 2.4 | 15 200 | 2.7 | 0.020 | 1940 | 3.8 | 29 700 | 3.0 | 0.041 | 3524 | 2.2 | 7454 | 2.5 | |
| C: Other comorbidities | 12 624 | 15.2 | 88 629 | 15.8 | 0.015 | 7614 | 14.9 | 145 457 | 14.9 | 0.002 | 22 032 | 13.4 | 41 967 | 14.2 | |
| Unknown | 112 | 0.1 | 941 | 0.2 | 0.008 | 112 | −0.2 | 1744 | −0.2 | 0.009 | … | … | … | … | |
| Low birth weight | 4146 | 5.0 | 28 536 | 5.1 | 0.003 | 4035 | 7.9 | 64 757 | 6.6 | 0.047 | 7374 | 4.5 | 13 815 | 4.7 | 0.008 |
| Gestational age | | | | | 0.023 | | | | | 0.067 | | | | | 0.075 |
| <29 weeks | 406 | 0.5 | 3130 | 0.6 | | 663 | 1.3 | 8233 | 0.8 | | 558 | 0.3 | 249 | 0.1 | |
| 29–31 weeks | 550 | 0.7 | 4191 | 0.7 | | 649 | 1.3 | 9668 | 1.0 | | 334 | 0.2 | 529 | 0.2 | |
| 32–36 weeks | 6440 | 7.8 | 44 148 | 7.9 | | 5195 | 10.1 | 92 826 | 9.5 | | 9864 | 6.0 | 17 199 | 5.8 | |
| Full term, >36 weeks | 50 906 | 61.5 | 339 569 | 60.5 | | 30 094 | 58.7 | 565 602 | 58.1 | | 101 525 | 62.0 | 185 461 | 62.5 | |
| Preterm, unknown GA | 1467 | 1.8 | 10 054 | 1.8 | | 854 | 1.7 | 16 108 | 1.7 | | 4136 | 2.5 | 9758 | 3.3 | |
| Unknown GA | 23 030 | 27.8 | 160 225 | 28.5 | | 13 774 | 26.9 | 281 620 | 28.9 | | 47 461 | 29.0 | 83352 | 28.1 | |
| Plan type | | | | | **0.415** | | | | | **0.342** | | | | | **0.114** |
| Comprehensive/ indemnity | 701 | 0.8 | 8002 | 1.4 | | 12 320 | 24.0 | 362 639 | 37.2 | | 4 | 0.0 | 21 | 0.0 | |
| EPO/PPO | 37 696 | 45.5 | 295 932 | 52.7 | | 43 | 0.1 | 758 | 0.1 | | 19 928 | 12.2 | 31 149 | 10.5 | |

**Table 1. Continued**

| | MarketScan Commercial (n = 644 116) | | | | | MarketScan Medicaid (n = 1 025 286) | | | | | Optum Clinformatics (n = 460 426) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | LTFU (n = 82 799) | | Not LTFU (n = 561 317) | | | LTFU (n = 51 229) | | Not LTFU (n = 974 057) | | | LTFU (n = 163 878) | | Not LTFU (n = 296 548) | | |
| Variable | No. | % | No. | % | SMD[b] | No. | % | No. | % | SMD | No. | % | No. | % | SMD |
| POS/POS with capitation | 21 004 | 25.4 | 60 648 | 10.8 | | … | … | … | … | | 81 074 | 49.5 | 146 406 | 49.4 | |
| HMO | 9702 | 11.7 | 61 413 | 10.9 | | 38 858 | 75.9 | 597 346 | 61.3 | | 17 145 | 10.5 | 26 685 | 9.0 | |
| CDHP/HDHP | 11 686 | 14.1 | 122 687 | 21.9 | | … | … | … | … | | 45 166 | 27.6 | 89 434 | 30.2 | |
| Missing/unknown | 2010 | 2.4 | 12 635 | 2.3 | | 8 | 0.0 | 13 314 | 1.4 | | 561 | 0.3 | 2853 | 1.0 | |
| Preseason LRTI, sensitive definition | 401 | 0.5 | 3143 | 0.6 | 0.010 | 637 | 1.2 | 8877 | 0.9 | 0.032 | 388 | 0.2 | 1385 | 0.5 | 0.039 |
| Hemodynamically significant CHD | 1700 | 2.1 | 12 991 | 2.3 | 0.018 | 1420 | 2.8 | 23 416 | 2.4 | 0.023 | 2804 | 1.7 | 6558 | 2.2 | 0.036 |
| Chronic lung disease | 356 | 0.4 | 3001 | 0.5 | 0.015 | 508 | 1.0 | 6764 | 0.7 | 0.033 | 413 | 0.3 | 1190 | 0.4 | 0.026 |
| Any chronic condition[d] | 7889 | 9.5 | 58 081 | 10.3 | 0.027 | 4045 | 7.9 | 76 636 | 7.9 | 0.001 | 13 620 | 8.3 | 27 865 | 9.4 | 0.038 |

Abbreviations: CDHP, consumer-driven health plan; CHD, congenital heart disease; EPO, exclusive provider organization; GA, gestational age; HDHP, high-deductible health plan; HMO, health maintenance organization; LTFU, lost to follow-up; MA RSV LRTI, medically attended respiratory syncytial virus lower respiratory tract infection; POS, point of service; PPO, preferred provider organization; SMD, standardized mean difference.

[a]Loss to follow-up differed slightly by the MA RSV LRTI definition in use. Quantities presented in the current table come from the analysis using the sensitive definition. Sample characteristics under the specific medically attended RSV LRTI definition are shown in the Supplementary Material.

[b]Standardized mean differences are unitless measures of similarity between the distributions of infants LTFU and not LTFU. SMDs highlighted in bold if > 0.1, indicating potentially meaningful differences between the selected analytic sample and infants who were not observed through the entirety of their first RSV season.

[c]Census division not available in MarketScan Medicaid data set.

[d]Includes CLD and hemodynamically significant CHD.

each of these data sets, infants in comorbidity group B accounted for 4.0%, 3.8%, and 3.2% of diagnoses, respectively, while infants in comorbidity group C accounted for 21.0%, 17.6%, and 17.2% of diagnoses (Table 3).

### *Sensitive Definition*

Under the sensitive definition the results were similar. Comorbidity group A infants accounted for 75.5%, 78.3%, and 80.1% of MA RSV LRTI diagnoses in the MSC, MSM, and OC data sets, respectively. In each of these data sets, infants in comorbidity group B accounted for 4.2%, 4.3%, and 3.1% of diagnoses, respectively, while infants in comorbidity group C accounted for 20.3%, 17.4%, and 16.8% of diagnoses (Table 3).

## DISCUSSION

Our study found that the majority (up to 80%) of first MA RSV LRTI events during infants' first RSV season were attributable to otherwise healthy term infants. This finding was consistent across all 3 insurance claims data sets we analyzed, each representing a different subpopulation of infants in the United States. As expected, using the sensitive definition of MA RSV LRTI increased estimated outcome rates both overall and within comorbidity groups, and resulted in a higher share of diagnoses with the outpatient setting recorded as the highest level of care (Table 3). However, the estimated share of the overall burden of MA RSV LRTI attributable to each comorbidity group did not change substantially, again indicating that term infants without known comorbidities accounted for up to 80% of (first) MA RSV LRTI diagnoses during infants' first RSV season. Our overall findings in insurance claims data, using ICD-10 codes to identify RSV infections, echo those from studies describing children hospitalized with laboratory-confirmed RSV, where healthy term infants accounted for between approximately 70% and 84% of hospitalized RSV cases, varying by age [3, 9]. Notably, we found that the predominance of healthy term infants among those with MA RSV LRTI is not limited to the inpatient setting but occurs in the outpatient and emergency department settings as well. The fact that the majority of infants born in the United States are considered full-term and lack comorbidities placing them at high risk of complications from RSV, coupled with their nontrivial absolute risk of contracting RSV, leads to their predominance among children with MA RSV LRTI, and suggests that meaningfully reducing the public health burden of RSV would require including term infants in future prevention efforts.

Also consistent with prior literature, we found that relative to infants in other comorbidity groups, preterm infants with CLD and HS-CHD were at higher risk of severe RSV infection, defined by an MA RSV LRTI associated with an inpatient admission, during their first RSV season [2, 4–8]. We also found that the rates of outpatient diagnoses for MA RSV LRTI were comparable across comorbidity groups, a finding that was consistent across data sets. Misclassification of comorbidity group (see discussion of limitations below) could have artificially reduced apparent differences in MA RSV LRTI risk between

**Table 2. Weighted Rates of MA RSV LRTI per 10 000 Infants Born Between 1 April 2016 and 29 February 2020, Stratified by Insurance Claims Data Set, MA RSV LRTI Outcome Definition, Comorbidity Group, and Highest Level of Care[a]**

| | Specific[b] | | | | Sensitive[b] | | | |
|---|---|---|---|---|---|---|---|---|
| Comorbidity Group | Outpatient | Emergency Room | Inpatient | Total | Outpatient | Emergency Room | Inpatient | Total |
| Data set: MarketScan Commercial | | | | | | | | |
| A: 37+ term infants, otherwise healthy | 234.2 (230.3, 238.2) | 72.6 (70.4, 74.8) | 69.6 (67.4, 71.8) | 376.4 | 806.4 (799.3, 813.6) | 154.4 (151.2, 157.6) | 88.7 (86.3, 91.2) | 1049.5 |
| B: Palivizumab eligible | 10.4 (9.6, 11.3) | 3.2 (2.7, 3.7) | 6.4 (5.8, 7.1) | 20.0 | 35.2 (33.7, 36.8) | 9.3 (8.5, 10.1) | 14.4 (13.4, 15.4) | 58.9 |
| C: Other comorbidities | 57.3 (55.3, 59.5) | 19.3 (18.1, 20.5) | 28.5 (27.0, 30.0) | 105.1 | 197.7 (193.8, 201.5) | 44.4 (42.6, 46.3) | 40.1 (38.4, 41.9) | 282.2 |
| Total | 302.0 | 95.0 | 104.5 | 501.5 | 1039.3 | 208.1 | 143.2 | 1390.6 |
| Data set: MarketScan Medicaid | | | | | | | | |
| A: 37+ term infants, otherwise healthy | 289.4 (286.1, 292.8) | 191.0 (188.2, 193.7) | 95.6 (93.7, 97.6) | 576.0 | 798.7 (793.3, 804.1) | 505.7 (501.3, 510.1) | 129.7 (127.5, 132.0) | 1434.1 |
| B: Palivizumab eligible | 11.5 (10.8, 12.2) | 6.1 (5.6, 6.5) | 10.0 (9.4, 10.7) | 27.6 | 33.1 (32.0, 34.2) | 22.9 (22.0, 23.9) | 23.0 (22.1, 24.0) | 79.0 |
| C: Other comorbidities | 55.3 (53.9, 56.7) | 36.9 (35.7, 38.1) | 36.6 (35.4, 37.8) | 128.8 | 155.6 (153.2, 158.0) | 109.9 (107.8, 111.9) | 54.0 (52.6, 55.4) | 319.5 |
| Total | 356.2 | 233.9 | 142.2 | 732.4 | 987.4 | 638.5 | 206.7 | 1832.6 |
| Data set: Optum Clinformatics | | | | | | | | |
| A: 37+ term infants, otherwise healthy | 234.5 (228.7, 240.4) | 82.3 (78.9, 85.8) | 76.5 (73.3, 79.8) | 393.3 | 764.6 (754.5, 774.7) | 146.1 (141.7, 150.7) | 91.6 (88.1, 95.1) | 1002.3 |
| B: Palivizumab eligible | 6.7 (5.7, 7.8) | 2.5 (1.9, 3.1) | 6.5 (5.5, 7.6) | 15.7 | 24.3 (22.4, 26.2) | 6.1 (5.2, 7.1) | 9.0 (7.9, 10.3) | 39.4 |
| C: Other comorbidities | 42.4 (40.0, 45.0) | 17.6 (16.0, 19.2) | 25.2 (23.4, 27.1) | 85.2 | 147.8 (143.3, 152.4) | 32.5 (30.4, 34.7) | 30.0 (28.1, 32.1) | 210.3 |
| Total | 283.6 | 102.4 | 108.2 | 494.2 | 936.6 | 184.8 | 130.6 | 1252 |

Abbreviation: MA RSV LRTI, medically attended respiratory syncytial virus lower respiratory tract infection.

[a]Rates expressed per 10 000 infants at risk within each comorbidity group, calculated as the weighted number of cases in each cell over the sum of inverse probability weights among complete cases times 10 000. Parentheses depict 95% confidence limits.

[b]MA RSV LRTI outcome definition.

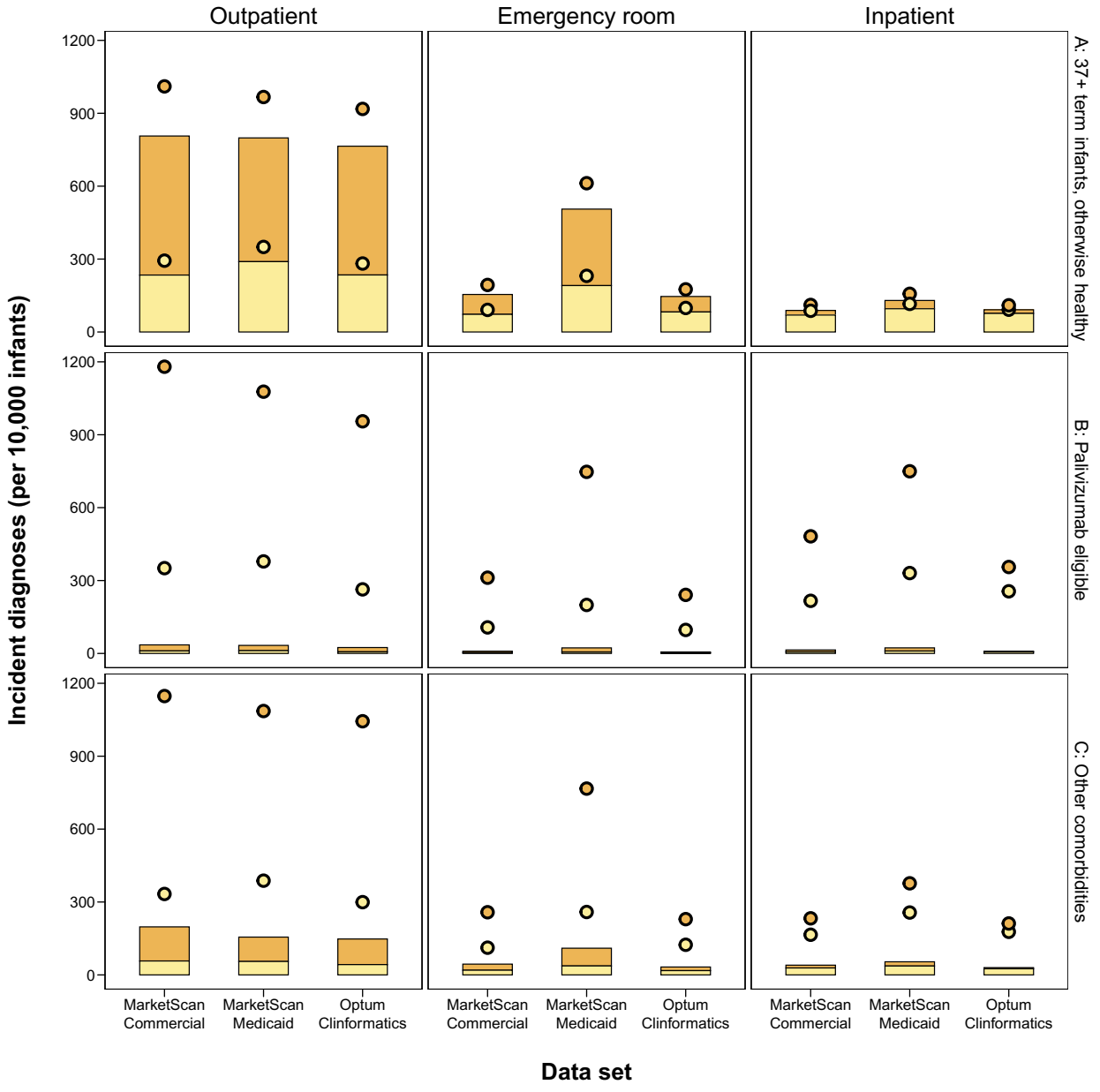


**Figure 1.** Weighted overall and comorbidity group-specific rates of medically attended respiratory syncytial virus lower respiratory tract infection (MA RSV LRTI) during infants' first RSV season, stratified by insurance claims data set, comorbidity group, and highest level of care associated with the first in-season MA RSV LRTI event. Bars encode the burden of MA RSV LRTI, defined as incident diagnoses per 10 000 infants at risk (denominator: sum of inverse probability of censoring weights among complete cases). The full height of each bar encodes burden under the sensitive definition, while the dark orange shading within the bar shows the marginal increase in estimated burden compared to the specific definition (pale orange). Points encode comorbidity group-specific rates per 10 000 infants at risk (denominator: sum of weights within comorbidity group among complete cases), where dark orange encodes analyses using the sensitive MA RSV LRTI definition and pale orange encodes analyses using the specific MA RSV LRTI definition. Estimates of burden illustrate the proportion of MA RSV LRTI cases attributable to each combination of comorbidity group and highest level of care (total burden within a dataset is the sum across 9 panels). Estimates of risk illustrate the likelihood of having an MA RSV LRTI diagnosis within each combination of comorbidity group and highest level of care. For instance, while the risk of an inpatient MA RSV LRTI is highest among comorbidity group B infants (location of points), these infants account for a small proportion of MA RSV LRTI cases during infants' first season (height of bars).

groups. Nonetheless, the heightened RSV risk among infants eligible for palivizumab might apply primarily to hospitalization.

Efforts to reduce RSV-related morbidity and mortality among infants in the United States have focused on risk-based strategies designed to prevent complications in preterm infants with comorbidities that predispose them to severe LRTIs [10, 11]. For instance, the recommendation that palivizumab be administered intramuscularly on a monthly basis to this subset of infants in order to reduce their risk of contracting RSV [10, 11],

**Table 3. Share of MA RSV LRTI Burden by Highest Level of Care and Comorbidity Group, Expressed as Specific % (Sensitive %)**

| Data Set | Comorbidity Group | Highest Level of Care | | | Total |
|---|---|---|---|---|---|
| | | Outpatient | Emergency Room | Inpatient | |
| MarketScan Commercial | A: 37+ term infants, otherwise healthy | 46.7 (58.0) | 14.5 (11.1) | 13.9 (6.4) | 75.0 (75.5) |
| | B: Palivizumab eligible | 2.1 (2.5) | 0.6 (0.7) | 1.3 (1.0) | 4.0 (4.2) |
| | C: Other comorbidities | 11.4 (14.2) | 3.8 (3.2) | 5.7 (2.9) | 21.0 (20.3) |
| | Total | 60.2 (74.7) | 19.0 (15.0) | 20.8 (10.3) | 100 (100) |
| MarketScan Medicaid | A: 37+ term infants, otherwise healthy | 39.5 (43.6) | 26.1 (27.6) | 13.1 (7.1) | 78.6 (78.3) |
| | B: Palivizumab eligible | 1.6 (1.8) | 0.8 (1.3) | 1.4 (1.3) | 3.8 (4.3) |
| | C: Other comorbidities | 7.5 (8.5) | 5.0 (6.0) | 5.0 (2.9) | 17.6 (17.4) |
| | Total | 48.6 (53.9) | 31.9 (34.8) | 19.4 (11.3) | 100 (100) |
| Optum Clinformatics | A: 37+ term infants, otherwise healthy | 47.5 (61.1) | 16.7 (11.7) | 15.5 (7.3) | 79.6 (80.1) |
| | B: Palivizumab eligible | 1.4 (1.9) | 0.5 (0.5) | 1.3 (0.7) | 3.2 (3.1) |
| | C: Other comorbidities | 8.6 (11.8) | 3.6 (2.6) | 5.1 (2.4) | 17.2 (16.8) |
| | Total | 57.4 (74.8) | 20.7 (14.8) | 21.9 (10.4) | 100 (100) |

Abbreviation: MA RSV LRTI, medically attended respiratory syncytial virus lower respiratory tract infection.

but not to other infants, is an approach targeted to an especially high-risk group to avoid the worst outcomes. Regardless of the reason for restricting an intervention to a particular subgroup, risk-based strategies may not be sufficient to reduce the burden of disease at the population level. Population-level prevention efforts such as vaccination, while they may sometimes focus on high-risk groups, are usually intended to reduce or suppress the overall burden of disease. Immunization products designed to prevent RSV are currently under development and may spur a renewed focus on reducing the RSV burden among all infants during their first RSV season. Quantifying the burden of disease attributable to various subgroups of infants and characterizing the medical care utilization associated with RSV infections are necessary precursors to developing sound guidelines for prevention efforts. The descriptive analyses we have presented provide such a population-level overview of the burden of MA RSV LRTI during infants' first RSV season, as well as the highest levels of care associated with these MA RSV LRTI diagnoses, and may be useful in tailoring future prevention efforts.

Our analyses are subject to several limitations. First, due to the paucity of laboratory data, we assessed MA RSV LRTI using ICD-10-CM codes, which, in the case of the specific definition, might have underestimated the overall burden of MA RSV LRTI. To account for the limitations of ICD-10-CM codes, we also used a sensitive definition that included codes for unspecified bronchiolitis, which might have overestimated the overall burden of MA RSV LRTI. Nonetheless, overall estimates of burden (and risk) may be conservative given the lack of systematic testing for RSV. Second, we were limited to approximating palivizumab eligibility via ICD-10-CM codes, which may have resulted in our misclassifying some infants' comorbidity groups. This issue likely affects comorbidity groups B and C more than group A and would be expected to attenuate between-group differences in estimated MA RSV LRTI risk. We also did not have data on whether infants received palivizumab. Third, we assumed that infants without explicit coding for preterm birth (either via ICD-10-CM or diagnosis-related group codes) were term infants. This assumption could have led to preterm infants being classified as term, which may have slightly attenuated the difference between infants in comorbidity group A versus those in groups B or C. Similarly, some infants assigned to comorbidity group A had diagnosis-related group codes indicating problems at birth but which included diagnoses that would not be considered causal risk factors for RSV. We assigned term infants to group C4 (term infants with select comorbidities, Supplementary Table 2) using ICD-10 codes assumed to affect RSV risk. Fourth, we made a birth hospitalization discharge a prerequisite to follow-up for outcome assessment and, in the OC data, used infants' admission date as a proxy for birth date. Preterm infants are more likely to have a longer birth hospitalization due to the need for supportive care, and thus, it is possible that using birth month to estimate IPCW, without also using date of discharge from the birth hospitalization, led to minor residual bias. Finally, while we used IPCW in an attempt to minimize selection bias that may have occurred due to common causes of loss to follow-up and MA RSV LRTI, unmeasured sources of selection bias may have affected our estimates of overall burden and comorbidity group-specific risk. Race/ethnicity, for instance, was either unavailable or was subject to a large degree of missingness. In addition, due to our inability to reliably link infants to their birth mothers, we could not weight estimates based on parental factors that might be stronger drivers of loss to follow-up than infant-level covariates. If such variables drove both loss of insurance eligibility and MA RSV LRTI among infants, our weighted estimates might be subject to residual selection bias [17]. In addition, using shrinkage or machine learning approaches to estimate inverse probability weights can, under some conditions (eg, data sparsity), inflate variance estimates and may induce bias [23]. Given the large size of our analytic

**Table 4. Weighted Comorbidity Group-Specific Rates of MA RSV LRTI During Infants' First RSV Season, Stratified by Insurance Claims Data Set, MA RSV LRTI Outcome Definition, Comorbidity Group, and Highest Level of Care Association With the MA RSV LRTI Event[a]**

| | Specific[b] | | | Sensitive[b] | | |
|---|---|---|---|---|---|---|
| Comorbidity Group | Outpatient | Emergency Room | Inpatient | Outpatient | Emergency Room | Inpatient |
| Data set: MarketScan Commercial | | | | | | |
| A: 37+ term infants, otherwise healthy | 293.5 (288.5, 298.5) | 90.9 (88.2, 93.8) | 87.2 (84.5, 89.9) | 1010.7 (1001.9, 1019.6) | 193.5 (189.5, 197.5) | 111.2 (108.1, 114.3) |
| B: Palivizumab eligible | 351.0 (323.1, 380.4) | 107.2 (91.9, 124.0) | 216.5 (194.6, 239.8) | 1179.9 (1130.5, 1230.5) | 311.7 (285.5, 339.4) | 482.0 (449.6, 515.9) |
| C: Other comorbidities | 333.0 (321.1, 345.1) | 112.0 (105.1, 119.2) | 165.3 (156.9, 174.0) | 1147.5 (1126.3, 1168.8) | 257.9 (247.4, 268.6) | 232.8 (222.9, 243.0) |
| Data set: MarketScan Medicaid | | | | | | |
| A: 37+ term infants, otherwise healthy | 349.9 (345.9, 354.0) | 230.9 (227.6, 234.2) | 115.6 (113.3, 118.0) | 966.9 (960.4, 973.4) | 612.2 (606.9, 617.5) | 157.1 (154.3, 159.8) |
| B: Palivizumab eligible | 378.7 (357.9, 400.2) | 199.6 (184.5, 215.5) | 330.8 (311.4, 351.0) | 1077.2 (1043.2, 1111.8) | 747.3 (718.6, 776.7) | 749.6 (720.8, 779.0) |
| C: Other comorbidities | 387.8 (377.9, 397.8) | 258.9 (250.8, 267.2) | 256.7 (248.7, 265.0) | 1085.9 (1070.0, 1102.0) | 766.7 (753.1, 780.4) | 376.9 (367.2, 386.7) |
| Data set: Optum Clinformatics | | | | | | |
| A: 37+ term infants, otherwise healthy | 281.6 (274.7, 288.6) | 98.8 (94.8, 103.0) | 91.9 (88.0, 95.6) | 917.8 (905.9, 929.9) | 175.4 (170.1, 180.9) | 109.8 (105.8, 114.2) |
| B: Palivizumab eligible | 263.8 (226.0, 305.3) | 96.7 (74.7, 122.5) | 255.7 (216.6, 299.0) | 955.4 (885.5, 1028.4) | 241.0 (205.9, 279.8) | 355.3 (310.3, 404.2) |
| C: Other comorbidities | 299.3 (282.2, 316.9) | 124.0 (113.2, 135.5) | 177.7 (165.0, 191.1) | 1043.7 (1013.3, 1074.6) | 229.5 (214.9, 244.7) | 212.1 (198.3, 226.5) |

Abbreviation: MA RSV LRTI, medically attended respiratory syncytial virus lower respiratory tract infection.

[a]Rates expressed per 10 000 infants at risk within each comorbidity group, calculated as the weighted number of cases within each cell over the sum of inverse probability weights within each comorbidity group times 10 000. Parentheses depict 95% confidence limits.

[b]MA RSV LRTI definition.

samples and elastic net models' ability to handle extreme data sparsity [19, 20], we do not believe these caveats apply to our weighting approach.

## CONCLUSION

Term infants without known comorbidities drive the burden of MA RSV LRTI among infants in their first RSV season in the United States. Future prevention efforts aimed at reducing the overall burden of RSV should consider all infants.

### Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online (http://jid.oxfordjournals.org/). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

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