Estimating the burden of adult hospitalized RSV infection using local and state data - methodology

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\textbf{ABSTRACT}

Respiratory syncytial virus (RSV) is becoming increasingly recognized as a serious threat to vulnerable population subgroups. This study describes the statistical analysis plan for a retrospective cohort study of adults hospitalized for acute respiratory infection (ARI) to estimate the population burden of RSV especially for groups such as the elderly, pregnant women and solid organ transplant patients. Disease burden estimates are essential for setting vaccine policy, e.g., should RSV vaccine become available, burden estimates may inform recommendations to prioritize certain high-risk groups. The study population is residents of Allegheny County, Pennsylvania ≥18 years of age who were hospitalized in Pennsylvania during the period September 1, 2015–August 31, 2018. Data sources will include U.S. Census, Pennsylvania Health Care Cost Containment Council (PHC4) and the electronic medical record for the health system to which the hospitals belong. The algorithm involves: 1) ARI-associated hospitalizations in PHC4 data; 2) adjustment for ARI hospitalizations among county residents but admitted to hospitals outside the county; and 3) RSV detections from respiratory viral panels. Key sensitivity analyses will adjust for undertaking for viruses in the fall and spring quarters. The results will be population-based estimates, stratified by age and risk groups. Adjusting hospitalization data using a multiplier method is a simple means to estimate the impact of RSV in a given area. This algorithm can be applied to other health systems and localities to estimate RSV and other respiratory pathogen burden in adults, to estimate burden following introduction of RSV vaccine and to make cost-effectiveness estimates.

\textbf{Introduction}

Respiratory syncytial virus (RSV) is a highly contagious respiratory virus that can result in bronchiolitis, otitis media, upper respiratory tract infections, and pneumonia.\textsuperscript{1} The virus was first isolated in young children over 60 years ago and much is known about its epidemiology and burden among the very young. Some decades later, documentation of the impact of RSV on morbidity and mortality of adults, especially older adults began. Advanced age and presence of high-risk medical conditions, especially cardiopulmonary disease, are known risk factors for severe RSV outcomes.\textsuperscript{2} RSV is estimated to cause 12\% of acute respiratory illness (ARI) visits\textsuperscript{3} and 7\% of influenza like illness (ILI)-ARI in the U.S. in adults over age 50 years.\textsuperscript{4} An estimated 3–7\% of older adults and 4–10\% of high risk adults contract RSV infections each year in the U.S.,\textsuperscript{5} numbers which rise with increasing age.\textsuperscript{5} Moreover, detections of RSV in hospitalized patients have increased steadily between 1997 and 2012, especially among those ≥60 years of age.\textsuperscript{6} CDC estimates that there are 177,000 adult RSV-associated hospitalizations in the U.S. annually. RSV has been estimated to account for 11\% percent of hospitalizations for pneumonia and chronic obstructive pulmonary disease exacerbations among elderly and high-risk adults during the RSV season.\textsuperscript{5} Hospitalized adults with RSV typically stay 3–6 days and frequently require mechanical ventilation and intensive care admission.\textsuperscript{3} The majority of RSV-associated deaths occur in adults >65 years (estimated at 14,000/year);\textsuperscript{7} RSV mortality also increases with increasing age,\textsuperscript{6} and particularly, among those who are compromised by chronic respiratory and cardiovascular diseases, such as COPD, those with transplants and other immunocompromising conditions,\textsuperscript{8} and adults requiring chronic immunosuppressive treatments for rheumatological conditions and solid tumors.\textsuperscript{9}

To date, there is no RSV vaccine available for use in either children or adults, although there are many in development.\textsuperscript{10} Except for use of monoclonal antibodies in premature infants, there is also no method of attenuating its severity through antiviral or other medication.

Accurate estimates of RSV burden are essential for healthcare planning, resource allocation and vaccine policy. RSV burden studies have primarily focused on children and, while similar studies of adults are becoming more common, there are still relatively few from the U.S.\textsuperscript{11} Of those included in reviews and meta-analyses\textsuperscript{4,12,13} only a subset includes younger adults or those with specific high-risk conditions. Surveillance-based studies with laboratory confirmation of RSV infection to calculate RSV burden can be resource intensive. Alternatively, statistical modeling strategies and multi-regression time-series to assess the burden of disease have
the advantages of being able to control for influenza, which presents with similar symptoms and co-circulates with RSV, and add a secular polynomial component of time to estimate the burden of RSV infection in adults.\textsuperscript{14–17} A simple approach that will provide more generalizable, more accurate, and more precise estimates is possible if population-wide data are available.

Herein, we describe the statistical analysis plan that will be used to produce population-based estimates of RSV burden using data from a large health system supplemented by statewide hospitalization data. This method was developed to facilitate burden estimates in situations where individual data are not available. This proposed multiplier method has the advantages of being simple, straightforward, able to account for adjustment factors, and can be used to estimate burden for an array of risk groups. Furthermore, should a RSV vaccine become available, this method may be used to compare RSV burden following introduction of the vaccine.

**Methods**

The University of Pittsburgh IRB has determined that the calculation of burden estimates is not human research, therefore approval is not necessary. The methods described herein will be used for a retrospective aggregate cohort study to evaluate the epidemiology and burden of RSV infection in adults (≥18 years of age) over three seasons in Allegheny County, Pennsylvania. The methods allow estimates to be calculated overall and for subtypes of RSV infection and population subgroups.

**Data**

The cohort will be defined as adult (≥18 years old) residents of Allegheny County Pennsylvania (PA) who were hospitalized in PA between September 1, 2015 and August 31, 2018. All data will be requested and reported across a series of cohort subgroups for which we will request either total counts or average values. Each hospital admission for a given individual will be included.

We will obtain retrospective data from three sources: 1) U.S. Census; 2) Pennsylvania Healthcare Cost Containment Council (PHC4); and 3) University of Pittsburgh Clinical Translational Science Institute (CTSI)’s Health Record Research Request (R3) system that draws data from the health system’s electronic medical record (EMR). U.S. Census estimates for Allegheny County, PA as of July 1, 2017 will be used to obtain the number of adult county residents as the denominator for overall burden estimate, where the numerator will be the adjusted number of RSV cases from county residents of the surveillance area. Residency will be established through the individual’s home zip code, using those codes listed online for Allegheny County.

Statewide hospitalization data on adult Allegheny County residents from PHC4 will be used. A hospitalization is defined generally, as an encounter for which admission orders are written. For this study, a hospital admission is defined specifically by criteria of the Centers for Disease Control and Prevention (CDC) National Healthcare Safety Network (NSHN; see Appendix Table A1). Admissions to specialty hospitals such as psychiatric or rehabilitation institutions will be excluded from the analysis.

PHC4 will provide data in aggregate for 3-month periods. The 3-month historical segments were selected to best reflect the active RSV season of September through May. The first segment will be September-November 2015, followed by successive segments from December-February, March-May, and June-August through August 2018. These aggregated data contain variables that will allow subgroup analyses, such as age, residency, high-risk conditions, etc. Admitting diagnoses and respiratory viral panel (RVP) findings on any adult Allegheny County resident who was hospitalized in the health system will be obtained through R3. Findings from repeat RVPs during a single admission will be collapsed into a single variable coded as a positive finding of RSV on any RVP performed (RSV = yes/no).

**Sample size**

A sample size calculation was performed to ensure that the selected health system and county datasets were sufficiently large to provide adequate power to achieve the desired outcome. We used a two-sided exact proportion test with a significance level of set at $\alpha = 0.05$, RSV positivity rate ranging from 0.06 to 0.09, and RVP positive sample size $n = 500$ to achieve adequate power.\textsuperscript{18–20} Table 1 shows the power for various values of the proportion of RSV cases under the alternative hypothesis and for different population sizes using the normal approximation method. Assuming a population size (i.e., the number of patients who had an RVP) of 1500 and a 7% RSV positivity rate, the study would be adequately powered with 105 RSV cases. A sample size of 1500 achieves 90% power to detect a difference of 0.02 using a two-sided $Z$-test with a significance level of 0.05. These results assume that the population proportion of RSV cases under the null hypothesis is 0.05.

Statistical tests and confidence intervals will be two-sided. Estimates will be presented with 95% confidence intervals, not testing the significance of the estimates.

**Calculating RSV population burden**

RSV hospitalization burden = RSV hospitalized cases per 100,000 adult residents. The calculation of burden has five steps. Table 2 lists the variables used in the equations and their definitions.

Step 1: Obtain from PHC4 the number of annual acute respiratory illness (ARI) hospitalizations for Allegheny County residents in Allegheny County hospitals ($ARI_{ACYear}$).

Step 2: Create an adjustment for out-of-county hospitalizations in the state using PHC4 data by calculating the proportion of ARI hospitalizations of Allegheny County residents in

**Table 1.** Estimated power for a given proportion of RSV positive RVP tests.

| Number of RVP tests | Proportion of RSV positive RVPs |
|---------------------|--------------------------------|
|                     | 0.06 | 0.07 | 0.08 | 0.09 |
| 1000                | 0.35 | 0.83 | 0.98 | 0.99 |
| 1500                | 0.42 | 0.90 | 0.99 | 0.99 |
| 2000                | 0.49 | 0.95 | 0.99 | 0.99 |
| 2500                | 0.74 | 0.95 | 1    | 1    |
### Variables used in RSV hospitalization burden estimate calculations.

| Variable                        | Definition                                                                 | Source       |
|---------------------------------|---------------------------------------------------------------------------|--------------|
| **Base analyses**               |                                                                           |              |
| \( \text{ARI}_{AC\text{Year}} \) | Number of ARI hospitalizations of Allegheny County residents admitted to Allegheny County hospitals during the year | PHC4         |
| \( \text{ARI}_{PA\text{Year}} \) | Number of ARI hospitalizations of Allegheny County residents admitted to all Pennsylvania hospitals during the year | PHC4         |
| \( \text{P}_{\text{ARI}_{AC}} \) | Proportion of ARI hospitalizations of Allegheny County residents in Allegheny County, PA, compared to all Pennsylvania hospitals | Calculated   |
| \( \text{aARI}_{AC\text{Year}} \) | Adjusted number of ARI hospitalizations of Allegheny County residents admitted to Allegheny County hospitals during the year | Calculated   |
| \( \text{RVP}_{RSV} \) | Number of RVPs performed in health system, after accounting for duplicate tests within a time period, such as 2 weeks | R3           |
| \( \text{RVP}_{All} \) | Number of RVPs performed in health system, after accounting for duplicate tests within a time period, such as 2 weeks | R3           |
| \( \text{P}_{\text{RSV}_{All}} \) | Proportion of RVP tests that are positive for RSV | Calculated   |
| \( \text{RSV}_{AC\text{Year}} \) | Number RSV cases in Allegheny County hospitals during the year | Calculated   |
| \( \text{Pop}_{AC} \) | Total population of Allegheny County | U.S. Census  |
| \( \text{RSV}_{AC\text{BurdenYear}} \) | RSV hospitalization burden per 100,000 persons in Allegheny County hospitals during the entire year | Calculated   |
| **Sensitivity analyses**        |                                                                           |              |
| \( \text{ARI}_{Q} \) | Number of ARI hospitalizations of Allegheny County residents admitted to health system Allegheny County hospitals during a given quarter | PHC4         |
| \( \text{RVP}_{Q} \) | Number RVP tests in the health system in Allegheny County in a quarter | R3           |
| \( \text{RSV}_{Q} \) | Number RSV positive RVP tests in the health system in Allegheny County in a quarter | R3           |
| \( \text{RVP}_{\text{FRact}_{Q}} \) | Fraction of RVPs performed in a given quarter | Calculated   |

Allegheny County hospitals, compared to all Pennsylvania hospitals for a given time period, in this case, one year. The outcome is used in the adjustment variable in Equation (2).

\[
\text{PrARI}_{AC} = \frac{\text{ARI}_{AC\text{Year}}}{\text{ARI}_{PA\text{Year}}} \tag{1}
\]

Calculate adjusted \( \text{ARI}_{AC\text{Year}} \):

\[
\text{aARI}_{AC\text{Year}} = \frac{\text{ARI}_{AC\text{Year}}}{\text{PrARI}_{AC}} \tag{2}
\]

In settings where this variable is directly available, the adjustment simplifies to \( \text{ARI}_{PA\text{Year}} \).

Step 3: Calculate the proportion of respiratory viral panel (RVP) tests from R3 for health system hospitals in Allegheny County that are positive for RSV. Repeat tests within a timeframe such as 2 weeks need to be removed so as not to inappropriately estimate viral burden.

\[
\text{PrRVP}_{RSV} = \frac{\text{RVP}_{RSV}}{\text{RVP}_{All}} \tag{3}
\]

Step 4: Estimate the crude number of RSV hospitalizations in Allegheny County by multiplying the number of ARI hospitalizations by the proportion of RSV positive RVP tests from R3 for health system hospitals in Allegheny County.

\[
\text{RSV}_{AC\text{Year}} = \text{aARI}_{AC\text{Year}} \times \text{PrRVP}_{RSV} \tag{4}
\]

Step 5: Calculate the RSV burden in Allegheny County during the year by dividing the adjusted RSV burden by the adult population of Allegheny County and multiplying by 100,000.

\[
\text{RSV}_{AC\text{BurdenYear}} = \frac{\text{RSV}_{AC\text{Year}}}{\text{Pop}_{AC}} \times 100,000 \tag{5}
\]

U.S. Census estimate for Allegheny County was 1,222,344 for 2017 of whom 974,362 (80%) were adults aged ≥18 years.

ARI hospitalizations include pneumonia and similar respiratory diseases. RSV and other respiratory viruses can also cause exacerbations of asthma, chronic obstructive pulmonary disease and heart failure; these are termed "ARI-related hospitalizations.” Because the fraction associated with RSV may differ between ARI hospitalizations and ARI-related hospitalizations and because the overall incidence of ARI hospitalizations and ARI-related hospitalizations is likely to differ, data should be stratified by ARI and ARI-related before being inputted into Equations (1)–(5). These individual results should be combined to estimate the true RSV burden. For simplicity, in this example, ARI hospitalizations and ARI-related hospitalizations were not separated.

The same general approach can be used in 3-month increments to make quarterly burden determinations, using the same equations but substituting quarterly data from R3 and PHC4.

### Variance and 95% confidence estimates

Variance and 95% confidence intervals (CIs) were calculated by the following formulas:

\[
\text{VAR}(\text{aRSV}_{AC\text{Year}}) = \frac{1}{X} \times \text{VAR}(\frac{1}{X})
\]

where \( X = \text{PrARI}_{AC} \times \text{PrRVP}_{RSV} \).

\[
95\%CI = \text{aRSV}_{AC\text{Year}} \pm 1.96 \times \sqrt{\text{VAR}(\text{aRSV}_{AC\text{Year}})}
\]

Using the Taylor expansion of first order that \( \text{VAR}(\frac{1}{X}) \) be approximated to \( \frac{\text{VAR}(X)}{\mu^4} \) and \( \mu \) equals the mean of the random variable \( X \). Under certain conditions and with assumptions of mean and variance values, the approximation of \( \text{VAR}(\frac{1}{X}) = 1 \times 10^{-6} \). In general, the mean and variance of inverse normal distributions do not exist based on the law of total expectations.\(^{21}\)

### Subgroup or special population analyses

Equations (4) and (5) give the burden estimates for Allegheny County that can be used to estimate burden for each of the age groups and other stratifications. A subgroup or special population of interest can be defined by ICD criteria and data from PHC4 and R3 can be obtained for this special population. For instance, immunocompromised persons may be preferentially tested by RVP and RSV cases might be higher in this population. To calculate the
population burden, data from PHC4 would be used for Equations (1) and (2). Using the proportion of RSV for this population from R3 for Equation (4), the number of RSV cases in immunocompromised persons can be calculated. To determine RSV burden in this group, (Equation (5)), the number of immunocompromised Allegheny County residents would need to be estimated, using a data source such as the National Health Interview Survey.

Sensitivity analyses (SA) for undertesting respiratory infections in the health system in the fall and spring quarters

SA-Step 1: Create an adjustment to estimate effects of undertesting outside of the winter respiratory season, which is when most RVP testing occurs. Compute the UPMC Allegheny County RVP testing fraction for each quarter (Q), shown in Equation (6).

\[ \text{RVPFract}_Q = \frac{\text{RVP}_Q}{\text{ARI}_Q} \]  

SA-Step 2: Determine if this fraction is approximately equal across the fall (F), winter (W) and spring (S) quarters. If so, then sensitivity analyses are moot. If the testing fractions are not the same, then SA-Step 3 is needed. The definition of approximately equal is open to debate; we propose ≤5% difference as the criterion.

SA-Step 3: Determine if the proportion of RSV detected by RVP varies by season.

\[ \text{PrRSV}_Q = \frac{\text{RSV}_Q}{\text{RVPFract}_Q} \]  

If \( \text{PrRSV} \) does not vary across seasons, then sensitivity analyses are unnecessary. If the proportion of RSV varies (we propose by ≥5%) by season, then SA is needed.

SA-Step 4: Adjust fall and spring quarter numbers of RVPs for testing fraction. If we assume that RVP testing in the fall and spring is weighted more heavily to those with immunosuppressive conditions than in the winter, then we can adjust for this situation. If RSV occurred in summer, then it could be added as well but this is not the case in our locale.

\[ \text{aRVP}_F = \text{RVP}_F \times \frac{\text{RVP}_F}{\text{RVP}_F} \]  

\[ \text{aRVP}_S = \text{RVP}_S \times \frac{\text{RVP}_W}{\text{RVP}_S} \]  

Then addition across the 3 seasons of RSV yields:

\[ \text{aRSV}_\text{Year} = \text{aRVP}_F + \text{RSV}_W + \text{aRVP}_S \]  

In a similar manner, the number of RSV cases can be adjusted for fall and for spring to create a total across the quarters:

\[ \text{aRSV}_\text{Year} = \text{aRSV}_F + \text{RSV}_W + \text{aRSV}_S \]  

Finally, an adjusted proportion of RSV can be estimated:

\[ \frac{\text{aRSV}_\text{Year}}{\text{aRVP}_\text{Year}} \]  

Simulated results

The above equations were used to create simulated results for Allegheny County using U.S. Census population data for Allegheny County and a range of values for \( \text{PrRSV} \) and proportion of state ARI hospitalizations in the county shown in Tables 3 and 4. For example, when we assume that there are 75,000 ARI hospitalizations across the Commonwealth and 25% are in Allegheny County hospitals, and we assume that RSV cases represent 12% of all RVP tests, we calculate the RSV hospitalization burden for Allegheny County per 100,000 adult population would be 308/100,000 adult population.

Discussion

We have developed a simple, adaptable method for estimating RSV burden that can be generalized to other diseases and other locales, provided that adequate viral testing has been done. Equations (1)–(5) can be used to calculate RSV burden for an entire geographical region or for a specific hospital or hospital system within that region. This proposed method can also be used to calculate the burden estimates for any respiratory infection on which data are collected at the hospital or health system and state levels. Alternatively, it can be adapted for use in international settings where local and regional or provincial data are accessible. It can also be used for high-risk sub-populations, provided that the appropriate data are available. RSV burden estimates may be quite different in the season or two following the current coronavirus pandemic, in which RSV infections were radically reduced, thereby offering further insight into its epidemiology.
There is no generalized method currently in use to estimate disease burden across an array of data structures. A recent review of studies to estimate RSV burden across the globe concluded that the significant heterogeneity of methodologies was reflected in widely differing RSV burden estimates. Differences included the methods for case ascertainment; quality of and protocols for laboratory testing; reliance on influenza surveillance to estimate RSV burden and a relatively low number of studies of adults, especially older adults. Our method has the advantage of using population data that are not constrained by the weaknesses of surveillance samples, such as lack of representativeness.

Several burden estimation methods have been developed that attempt to adjust surveillance data for under-detection of the burden estimate for seasonal influenza in the Netherlands, pandemic A/H1N1 influenza and novel influenza A/H3N2 in the United States, and influenza A/H7N9 in China. The methods developed for those studies ranged from simple multipliers to more complex mathematical and statistical models, depending on setting and data availability. Our method does not require such adjustments because it depends on RSV-specific hospitalization data.

**Strengths and limitations**

Our method is subject to some limitations. It assumes that viruses causing hospital admission are the same for health system and non-health system hospitals in the county. Given that the health system has 60% of the market share in the county and includes both community and subspecialty hospitals, this is not unreasonable but the viral burden in other hospitals is an extrapolation. Given the higher burden of some viruses in immunocompromised and transplant patients, care is needed to make sure that both community hospitals and subspecialty hospital are included so as not to bias estimates one way or another. As mentioned in the methods, the mean and variance of the inverse of the random variables do not exist. Through the Taylor series of expansion, we get the approximations of these values that limit the width of the confidence bounds of the estimate. Study of the behavior of the density function of the normal random variable is beyond the scope this manuscript. If the magnitude of ARI data is underreported in PHC4, then we may overestimate RSV burden. Given that Allegheny County is an hour from the state border and that strong hospital systems exist within the county, the likelihood that substantive numbers of out-of-state hospitalizations that would be missed is low, except for those persons who split the year as residents of two different states. Viral detections may not always represent symptomatic infection but could represent asymptomatic infections or perhaps colonization; this topic is beyond the scope of the current paper to address and is an area for further research. Similarly, co-detections of multiple viruses may not represent symptomatic infection from all of those viruses but co-detections in adults are uncommon (5%–10%). Bacterial co-infections have been reported to account for 12% of RSV ARIs among hospitalized patients and 9.3% to 19.7% of RSV-associated pneumonias among hospitalized patients. These severe outcomes would need to be factored into any analysis of severity and consequential economic burden.

The association between grouped ICD codes in PHC4 and individual ICD codes from the EMR that are associated with RVP tests is unknown and cannot be adjusted for in this analysis. If the association between data sources were high (close to 1), actual RSV burden would be similar to calculated estimates; whereas, if the association were low, actual RSV burden would be higher than calculated estimates.

To reduce the complexity, we made estimates using the number of cases and RSV hospitalizations by quarter. There may be variations across seasons and age-specific subgroups, thus our expected burden estimates may not fully reflect the level of uncertainty. Burden may be underestimated or over-estimated if careful consideration of the correction multipliers is not made. The multiplier components should be recalculated for each season because the detection probabilities may vary by season.

The strength of this method is that it is not specific to the US healthcare system and can be applied in a variety of settings in which the number of ARI hospitalizations and the RSV positives within the boundaries of the area are available.

**Conclusions**

The proposed method is relatively a simple method for adjusting and generalizing data to estimate RSV disease burden and may be used in other population-based settings and for other respiratory diseases. When RSV vaccines become available, accurate and timely estimates of RSV burden in various population subgroups will be important factors to consider for RSV vaccination recommendations.

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**Authors’ contribution**

GBK contributed to the study design and was responsible for statistical analysis, drafting and editing the manuscript. MPN contributed to the study design, obtained grant funding, revised the manuscript and is the lead investigator. HE contributed to the study design, acquired data for this study from PHC4 and UPMC health plan and revised the manuscript. RZ contributed to the study design and revised the manuscript. All authors read and approved the final version.

**Abbreviations**

| Abbreviation | Full Form                              |
|-------------|----------------------------------------|
| ARI         | Acute Respiratory Infection            |
| CDC         | Centers for Disease Control and Prevention |
| CTSI        | Clinical Translational Science Institute |
EMR  Electronic medical record
NHSN  National Healthcare Safety Network
PHC4  Pennsylvania Health Care Cost Containment Council
R3  Health Record Research Request
RSV  Respiratory Syncytial Virus
RVP  Respiratory Viral Panel

Disclosure of potential conflicts of interest

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Appendix A

Table A1. List of ARI-specific and ARI-related (i.e. COPD, asthma, CHF) ICD-9/10 codes adapted from CDC's HAIVEN study.

| Category         | ICD10  | Description                                                                 | ICD9  | Description                                      |
|------------------|--------|-----------------------------------------------------------------------------|-------|--------------------------------------------------|
| ARI-specific     | A37.01 | Whooping cough due to Bordetella pertussis with pneumonia                   | 484.3 | Pneumonia in whooping cough                      |
| ARI-specific     | A37.11 | Whooping cough due to Bordetella parapertussis with pneumonia               |       |                                                  |
| ARI-specific     | A37.81 | Whooping cough due to other Bordetella species with pneumonia               |       |                                                  |
| ARI-specific     | A37.91 | Whooping cough, unspecified species with pneumonia                          |       |                                                  |
| ARI-specific     | B25.0  | Cytomegaloviral pneumonia                                                  | 484.1 | Pneumonia in cytomegalic inclusion disease       |
| ARI-specific     | B97.4  | Respiratory syncytial virus causing diseases class elswhr                   | 796   | Respiratory Syncytial Virus (Rsv)               |
| ARI-specific     | J00    | Acute nasopharyngitis [common cold]                                        | 460   | Acute nasopharyngitis [common cold]             |
| ARI-specific     | J01.00 | Acute maxillary sinusitis, unspecified                                      | 461.0 | Acute Maxillary Sinusitis                       |
| ARI-specific     | J01.01 | Acute recurrent maxillary sinusitis                                        | 461.1 | Acute frontal sinusitis                         |
| ARI-specific     | J01.10 | Acute recurrent maxillary sinusitis unspecified                             | 461.2 | Acute ethmoidal sinusitis                       |
| ARI-specific     | J01.20 | Acute ethmoidal sinusitis, unspecified                                      | 461.3 | Acute sphenoidal sinusitis                      |
| ARI-specific     | J01.30 | Acute recurrent sphenoidal sinusitis unspecified                            | 461.4 | Acute sphenoidal sinusitis                      |
| ARI-specific     | J01.40 | Acute pansinusitis, unspecified                                             | 461.5 | Other acute sinusitis                           |
| ARI-specific     | J01.41 | Acute recurrent pansinusitis                                                | 461.6 | Acute sinusitis, unspecified                    |
| ARI-specific     | J01.80 | Other acute sinusitis                                                       | 461.7 | Other acute sinusitis                           |
| ARI-specific     | J01.81 | Other acute recurrent sinusitis                                             | 461.8 | Other acute sinusitis                           |
| ARI-specific     | J01.90 | Acute sinusitis, unspecified                                                | 461.9 | Acute sinusitis, unspecified                    |
| ARI-specific     | J01.91 | Acute recurrent sinusitis, unspecified                                      | 462   | Acute pharyngitis                               |
| ARI-specific     | J02.0  | Streptococcal pharyngitis                                                  | 340   | Streptococcal pharyngitis                       |
| ARI-specific     | J02.8  | Acute pharyngitis due to other specified organisms                          | 462   | Acute pharyngitis                               |
| ARI-specific     | J02.9  | Acute pharyngitis, unspecified                                              | 463   | Acute tonsillitis                               |
| ARI-specific     | J03.00 | Acute streptococcal tonsillitis, unspecified                               |       |                                                  |
| ARI-specific     | J03.01 | Acute recurrent streptococcal tonsillitis                                  |       |                                                  |
| ARI-specific     | J03.80 | Acute tonsillitis due to other specified organisms                          |       |                                                  |
| ARI-specific     | J03.81 | Acute recurrent tonsillitis due to other specified organisms               |       |                                                  |
| ARI-specific     | J03.90 | Acute tonsillitis, unspecified                                              |       |                                                  |
| ARI-specific     | J03.91 | Acute recurrent tonsillitis, unspecified                                    |       |                                                  |
| ARI-specific     | J04.0  | Acute laryngitis                                                           | 464.3 | Acute laryngitis and tracheitis                 |
| ARI-specific     | J04.10 | Acute tracheitis without obstruction                                        |       |                                                  |
| ARI-specific     | J04.11 | Acute tracheitis with obstruction                                           |       |                                                  |
| ARI-specific     | J04.2  | Acute laryngotracheitis                                                    |       |                                                  |
| ARI-specific     | J04.30 | Supraglottitis, unspecified, without obstruction                           |       |                                                  |
| ARI-specific     | J04.31 | Supraglottitis, unspecified, with obstruction                              |       |                                                  |
| ARI-specific     | J05.0  | Acute obstructive laryngitis [croup]                                       |       |                                                  |
| ARI-specific     | J05.10 | Acute epiglottitis without obstruction                                      |       |                                                  |
| ARI-specific     | J05.11 | Acute epiglottitis with obstruction                                         |       |                                                  |
| ARI-specific     | J06.0  | Acute laryngopharyngitis                                                   | 465.0 | Acute laryngopharyngitis                        |
| ARI-specific     | J06.9  | Acute upper respiratory infection, unspecified                            | 465.8 | Acute upper respiratory infections of multiple sites |
| ARI-specific     |       |                                                                            | 465.9 | Acute upper respiratory infection of unspecified site |

(Continued)
| Category         | ICD10   | Description                                       | ICD9    | Description                                      |
|------------------|---------|---------------------------------------------------|---------|--------------------------------------------------|
| ARI-specific     | J09.X1  | Influenza due to ident novel A virus w pneumonia   | 487.*   | Influenza                                        |
| ARI-specific     | J09.X2  | Flu due to ident novel influenza A virus w oth resp | 488.*   | Influenza due to identified avian influenza virus|
| ARI-specific     | J09.X3  | Influenza due to ident novel A virus w GI manifest |         |                                                  |
| ARI-specific     | J09.X9  | Flu due to ident novel influenza A virus w oth manifest |       |                                                  |
| ARI-specific     | J10.00  | Flu due to oth ident flu virus w unspec type of pneumonia |       |                                                  |
| ARI-specific     | J10.01  | Flu due to oth ident flu virus w same oth ident flu virus pn |       |                                                  |
| ARI-specific     | J10.08  | Influenza due to oth ident influenza virus w oth pneumonia |       |                                                  |
| ARI-specific     | J10.1   | Flu due to oth ident influenza virus w oth resp manifest |       |                                                  |
| ARI-specific     | J10.2   | Influenza due to oth ident influenza virus w GI manifest |       |                                                  |
| ARI-specific     | J10.81  | Influenza due to oth ident influenza virus w encephalopathy |       |                                                  |
| ARI-specific     | J10.82  | Influenza due to oth ident influenza virus w myocarditis |       |                                                  |
| ARI-specific     | J10.83  | Influenza due to oth ident influenza virus w otitis media |       |                                                  |
| ARI-specific     | J10.89  | Influenza due to oth ident influenza virus w oth manifest |       |                                                  |
| ARI-specific     | J11.00  | Flu due to unidentified flu virus w unspec type of pneumonia |       |                                                  |
| ARI-specific     | J11.08  | Flu due to unidentified flu virus w specified pneumonia |       |                                                  |
| ARI-specific     | J11.1   | Flu due to unidentified influenza virus w oth resp manifest |       |                                                  |
| ARI-specific     | J11.2   | Influenza due to unidentified influenza virus w GI manifest |       |                                                  |
| ARI-specific     | J11.81  | Influenza due to unidentified influenza virus w encephalopathy |       |                                                  |
| ARI-specific     | J11.82  | Influenza due to unidentified influenza virus w myocarditis |       |                                                  |
| ARI-specific     | J11.83  | Influenza due to unidentified influenza virus w oth manifest |       |                                                  |
| ARI-specific     | J11.89  | Influenza due to unidentified influenza virus w oth manifest |       |                                                  |
| ARI-specific     | J12.0   | Adenoviral pneumonia                               | 480.0   | Adenoviral pneumonia                             |
| ARI-specific     | J12.1   | Respiratory syncytial virus pneumonia              | 480.1   | Respiratory syncytial virus pneumonia            |
| ARI-specific     | J12.2   | Parainfluenza virus pneumonia                      | 480.2   | Parainfluenza virus pneumonia                    |
| ARI-specific     | J12.3   | Human metapneumovirus pneumonia                   |         |                                                  |
| ARI-specific     | J12.81  | Pneumonia due to SARS-associated coronavirus       | 480.3   | Pneumonia due to SARS-associated coronavirus     |
| ARI-specific     | J12.89  | Other viral pneumonia                              | 480.8   | Other viral pneumonia                            |
| ARI-specific     | J12.9   | Viral pneumonia, unspecified                       | 480.9   | Viral pneumonia, unspecified                     |
| ARI-specific     | J13     | Pneumonia due to Streptococcus pneumonia           | 481     | Pneumonia due to Streptococcus pneumonia         |
| ARI-specific     | J14     | Pneumonia due to Hemophilus influenzae             | 482.2   | Pneumonia due to Hemophilus influenzae [H. influenzae] |
| ARI-specific     | J15.0   | Pneumonia due to Klebsiella pneumonia              | 482.0   | Pneumonia due to Klebsiella pneumonia            |
| ARI-specific     | J15.1   | Pneumonia due to Pseudomonas                       | 482.1   | Pneumonia due to Pseudomonas                     |
| ARI-specific     | J15.20  | Pneumonia due to staphylococcus, unspecfied        | 482.4   | Pneumonia due to staphylococcus, unspecfied      |
| ARI-specific     | J15.211 | Pneumonia due to methicillin suscep staph           | 482.4   | Pneumonia due to methicillin suscep staph        |
| ARI-specific     | J15.212 | Pneumonia due to Methicillin resistant Staphylococcus aureus |       | Methicillin resistant pneumonia due to other staphylococcus |
| ARI-specific     | J15.29  | Pneumonia due to other staphylococcus              | 482.4   | Pneumonia due to other staphylococcus            |
| ARI-specific     | J15.3   | Pneumonia due to streptococcus, group B            | 482.3   | Pneumonia due to Streptococcus, group B          |
| Category               | ICD10 | Description                                      | ICD9   | Description                                      |
|------------------------|-------|--------------------------------------------------|--------|--------------------------------------------------|
| ARI-specific           | J15.4 | Acute bronchitis due to other streptococci       | 482.3  | Pneumonia due to unspecified Streptococcus      |
| ARI-specific           | J15.5 | Pneumonia due to Escherichia coli                | 482.8  | Pneumonia due to Escherichia coli               |
| ARI-specific           | J15.6 | Pneumonia due to other aerobic Gram-negative bacteria | 482.8  | Pneumonia due to other gram-negative bacteria   |
| ARI-specific           | J15.7 | Pneumonia due to Mycoplasma pneumoniae           | 483.0  | Pneumonia due to Mycoplasma pneumoniae          |
| ARI-specific           | J15.8 | Pneumonia due to other specified bacteria         | 482.8  | Pneumonia due to other specified bacteria        |
| ARI-specific           | J15.9 | Unspecified bacterial pneumonia                  | 482.8  | Pneumonia due to anaerobes                      |
| ARI-specific           | J16.0 | Chlamydial pneumonia                             | 482.9  | Bacterial pneumonia, unspecified               |
| ARI-specific           | J16.8 | Pneumonia due to other specified infectious organisms | 483.1  | Pneumonia due to chlamydia                      |
| ARI-specific           | J17   | Pneumonia in diseases classified elsewhere        | 484.8  | Pneumonia in other infectious diseases classified elsewhere |
| ARI-specific           | J18.0 | Bronchopneumonia, unspecified organism            | 484.7  | Pneumonia in other systemic mycoses             |
| ARI-specific           | J18.1 | Lobar pneumonia, unspecified organism             | 485    | Bronchopneumonia, unspecified organism          |
| ARI-specific           | J18.2 | Hypostatic pneumonia, unspecified organism        | 486    | Other pneumonia, unspecified organism           |
| ARI-specific           | J18.8 | Other pneumonia, unspecified organism             | 487    | Other pneumonia, unspecified organism           |
| ARI-specific           | J18.9 | Pneumonia, unspecified organism                   | 488    | Pneumonia due to Legionella                     |
| ARI-specific           | J20.0 | Acute bronchitis due to Mycoplasma pneumoniae     | 482.8  | Pneumonia due to Legionella                     |
| ARI-specific           | J20.1 | Acute bronchitis due to Hemophilus influenzae     | 484.5  | Pneumonia in anthrax                            |
| ARI-specific           | J20.2 | Acute bronchitis due to streptococcus             | 484.6  | Pneumonia in aspergillus                        |
| ARI-specific           | J20.3 | Acute bronchitis due to coxsackievirus            | 466.0  | Acute Bronchitis                               |
| ARI-specific           | J20.4 | Acute bronchitis due to parainfluenza virus       | 466.1  | Acute bronchitis due to respiratory syncytial virus |
| ARI-specific           | J20.5 | Acute bronchitis due to respiratory syncytial virus | 466.1  | Acute bronchitis due to respiratory syncytial virus |
| ARI-specific           | J20.6 | Acute bronchitis due to rhinovirus               | 466.1  | Acute bronchitis due to respiratory syncytial virus |
| ARI-specific           | J20.7 | Acute bronchitis due to echovirus                | 519.8  | Other diseases of respiratory system, not elsewhere classified |
| ARI-specific           | J20.8 | Acute bronchitis due to other specified organisms | 519.9  | Unspecified disease of respiratory system       |
| ARI-specific           | J20.9 | Acute bronchitis, unspecified                     |        |                                                  |
| ARI-specific           | J21.0 | Acute bronchitis due to respiratory syncytial virus |        |                                                  |
| ARI-specific           | J21.1 | Acute bronchitis due to human metapneumovirus     |        |                                                  |
| ARI-specific           | J21.8 | Acute bronchitis due to other specified organisms |        |                                                  |
| ARI-specific           | J21.9 | Acute bronchitis, unspecified                     |        |                                                  |
| ARI-specific           | J22   | Unspecified acute lower respiratory infection     |        |                                                  |
| ARI-specific           | J39.8 | Other specified diseases of upper respiratory tract |        |                                                  |
| ARI-specific           | J39.9 | Disease of upper respiratory tract, unspecified   |        |                                                  |
| ARI-specific           | J40   | Bronchitis, not specified as acute or chronic     | 490    | Bronchitis, not specified as acute or chronic   |
| ARI-specific           | R05   | Cough                                            | 786.2  | Cough                                           |
| ARI-specific           | R06.00| Dyspnea, unspecified                            | 786.0  | Shortness of breath                             |
| ARI-specific           | R06.02| Shortness of breath                              |        |                                                  |
| ARI-specific           | R06.1 | Stridor                                          | 786.1  | Stridor                                         |
| ARI-specific           | R06.2 | Wheezing                                         | 786.2  | Wheezing                                        |
| ARI-specific           | R06.82| Tachypnea, not elsewhere classified              | 786.0  | Tachypnea                                       |
| Category       | ICD10 | Description                                | ICD9  | Description                                      |
|---------------|-------|--------------------------------------------|-------|-------------------------------------------------|
| ARI-specific  | R09.02| Hypoxemia                                  | 799.0 | Hypoxemia                                        |
| ARI-specific  | R09.2 | Respiratory arrest                         | 799.1 | Respiratory arrest                               |
| ARI-specific  | R09.7 |                | 786.0 | Other dyspnea and respiratory abnormality       |
| ARI-related   | J45.20| Mild intermittent asthma, uncomplicated    |       |                                                 |
| ARI-related   | J45.21| Mild intermittent asthma with (acute) exhaustion |       |                                                 |
| ARI-related   | J45.30| Mild persistent asthma, uncomplicated      |       |                                                 |
| ARI-related   | J45.31| Mild persistent asthma with (acute) exhaustion |       |                                                 |
| ARI-related   | J45.32| Mild persistent asthma with status asthmaticus |       |                                                 |
| ARI-related   | J45.40| Moderate persistent asthma, uncomplicated  |       |                                                 |
| ARI-related   | J45.41| Moderate persistent asthma with (acute) exhaustion |       |                                                 |
| ARI-related   | J45.42| Moderate persistent asthma with status asthmaticus |       |                                                 |
| ARI-related   | J45.50| Severe persistent asthma, uncomplicated    |       |                                                 |
| ARI-related   | J45.51| Severe persistent asthma with (acute) exhaustion |       |                                                 |
| ARI-related   | J45.52| Severe persistent asthma with status asthmaticus |       |                                                 |
| ARI-related   | J45.901| Unspecified asthma with (acute) exacerbation |       |                                                 |
| ARI-related   | J45.902| Unspecified asthma with status asthmaticus |       |                                                 |
| ARI-related   | J45.909| Unspecified asthma, uncomplicated          |       |                                                 |
| ARI-related   | J45.990| Exercise induced bronchospasm              |       |                                                 |
| ARI-related   | J45.991| Cough variant asthma                       |       |                                                 |
| ARI-related   | J45.998| Other asthma                               |       |                                                 |
| ARI-related   | ISO.1 | Left ventricular failure                  | 428.* | Congestive heart failure                        |
| ARI-related   | ISO.20| Unspecified systolic (congestive) heart failure |       |                                                 |
| ARI-related   | ISO.21| Acute systolic (congestive) heart failure  |       |                                                 |
| ARI-related   | ISO.22| Chronic systolic (congestive) heart failure|       |                                                 |
| ARI-related   | ISO.23| Acute on chronic systolic (congestive) heart failure |       |                                                 |
| ARI-related   | ISO.30| Unspecified diastolic (congestive) heart failure |       |                                                 |
| ARI-related   | ISO.31| Acute diastolic (congestive) heart failure  |       |                                                 |
| ARI-related   | ISO.32| Chronic diastolic (congestive) heart failure |       |                                                 |
| ARI-related   | ISO.33| Acute on chronic diastolic (congestive) heart failure |       |                                                 |
| ARI-related   | ISO.40| Unsp combined systolic and diastolic (congestive) hrt fail |       |                                                 |
| ARI-related   | ISO.41| Acute combined systolic and diastolic (congestive) hrt fail |       |                                                 |
| ARI-related   | ISO.42| Chronic combined systolic and diastolic hrt fail |       |                                                 |
| ARI-related   | ISO.43| Acute on chronic combined systolic and diastolic hrt fail |       |                                                 |
| ARI-related   | ISO.810| Right heart failure, unspecified          |       |                                                 |
| ARI-related   | ISO.811| Acute right heart failure                 |       |                                                 |
| ARI-related   | ISO.812| Chronic right heart failure               |       |                                                 |
| ARI-related   | ISO.813| Acute on chronic right heart failure       |       |                                                 |
| ARI-related   | ISO.814| Right heart failure due to left heart failure |       |                                                 |
| ARI-related   | ISO.82| Biventricular heart failure                |       |                                                 |
| ARI-related   | ISO.83| High output heart failure                 |       |                                                 |
| ARI-related   | ISO.84| End stage heart failure                   |       |                                                 |
| ARI-related   | ISO.89| Other heart failure                       |       |                                                 |
| ARI-related   | ISO.9 | Heart failure, unspecified                |       |                                                 |
| ARI-related   | J41.0 | Simple chronic bronchitis                 | 491.0 | Simple chronic bronchitis                       |
| ARI-related   | J41.1 | Mucopurulent chronic bronchitis           | 491.1 | Mucopurulent chronic bronchitis                 |
| ARI-related   | J41.8 | Mixed simple and mucopurulent chronic bronchitis | 491.8 |                                                 |

(Continued)
| Category       | ICD10 | Description                                | ICD9 | Description                                |
|----------------|-------|--------------------------------------------|------|--------------------------------------------|
| ARI-related    | J42   | Unspecified chronic bronchitis             | 491.9| Unspecified chronic bronchitis             |
| ARI-related    | J43.0 | Unilateral pulmonary emphysema             | 492.8| Other emphysema                            |
| ARI-related    | J43.1 | Panlobular emphysema                       |      |                                            |
| ARI-related    | J43.2 | Centrilobular emphysema                    |      |                                            |
| ARI-related    | J43.8 | Other emphysema                            |      |                                            |
| ARI-related    | J43.9 | Emphysema, unspecified                     |      |                                            |
| ARI-related    | J44.0 | Chronic obstructive pulmonary disease w acute lower resp infct | 491.2| Obstructive chronic bronchitis, without exacerbation |
| ARI-related    | J44.1 | Chronic obstructive pulmonary disease w (acute) exacerbation |      | Obstructive chronic bronchitis, with (acute) exacerbation |
| ARI-related    | J44.9 | Chronic obstructive pulmonary disease, unspecified |      | Obstructive chronic bronchitis with acute bronchitisChronic airway obstruction, not elsewhere classified (includes COPD NOS) |

*Take ALL codes under the root number.