Respiratory Syncytial Virus in Older Adults: A Hidden Annual Epidemic

A Report by the National Foundation for Infectious Diseases
Overview

Respiratory syncytial virus (RSV) is a common cause of acute respiratory illness in older adults, with the risk of serious infection increasing with age.\textsuperscript{1-4} The virus circulates along with many other winter respiratory viruses, most notably seasonal influenza, and is largely indistinguishable from influenza based on clinical presentation alone.\textsuperscript{2,5,6} RSV is second only to influenza as a cause of medically significant respiratory tract illnesses in adults\textsuperscript{7,8} and is estimated to cause 177,000 hospitalizations and 14,000 annual deaths in US adults age 65 years and older.\textsuperscript{2,9}

There is no specific treatment for RSV in adults and currently no licensed vaccine to prevent the disease. However, several promising candidate vaccines are on the horizon to protect populations at increased risk of serious RSV outcomes, including older adults.\textsuperscript{10} RSV epidemiology and burden of disease suggest vaccines should target infants younger than age six months, infants and children age six to 24 months, pregnant women (to provide passive immunity to newborns), and adults age 65 years and older.\textsuperscript{11} The focus of this report is on the older adult population.

Recognizing and defining the impact of RSV in older adults is important in order to evaluate the impact of new prevention and treatment options that will likely be available in the US soon.”

– William Schaffner, MD
RSV: A Pervasive Infection with Lifelong Reinfections

RSV is an RNA virus that was isolated in the mid-1950s from a captive chimpanzee with upper respiratory tract illness. It is classified in the Paramyxoviridae family, which includes parainfluenza, meta-pneumovirus, and measles viruses. Humans are the only known reservoir.

RSV subtypes A and B co-circulate. Some data indicate that RSV subtype A may cause more severe disease. Two surface glycoproteins, F and G, are responsible for initiation and propagation of RSV infection in the host. The G protein differs on the RSV A and B subtypes, but the F protein is antigenically stable with minimal difference between subtypes (Figure 1).

RSV epidemics occur annually during the winter months in temperate regions, with most US infections occurring in a 22-week period from November to May. By age two years, almost all children have been infected with RSV and about half have been infected twice. Immunity is fleeting and reinfection is common throughout the lifespan.

Hall and colleagues challenged 15 healthy young adults with RSV at two, four, eight, 14, 20, and 26 months following natural infection. The rate of reinfection was highest after the first challenge (~50 percent) showing that just two months after RSV infection, otherwise healthy adults were already susceptible to reinfection. The cumulative reinfection rate was two-thirds by eight months and over the course of the approximately two-year study, 73 percent had two or more and 47 percent had three or more infections.

Pathogenesis

The pathogenesis of disease associated with RSV is well described in young children, but little is known about the pathogenesis in older adults. In children, RSV usually begins as an infection in the nasal mucosal epithelial cells. The RSV virion attaches to and penetrates ciliated nasal epithelial cells by fusing with the cell membrane, entering, and replicating in the cytoplasm. Infectious virus buds from and exits the infected cells via apical membrane on the lumenal side (the same side of entry) of the airway, and is not released into the systemic circulation through the basement membrane. This restricted replication may be why RSV is not a systemic virus, making it difficult for the immune system to mount a very strong and durable systemic response.
Virus replication results in epithelial-cell sloughing, inflammatory cell infiltration, edema, increased mucous secretion, and impaired ciliary action. The sloughed cells create an obstruction; during inhalation the airway opens, but on exhalation when the lungs deflate, the airway can become obstructed, causing air trapping and wheezing.

**RSV Disease: Age-Related Severity**

RSV is associated with the most severe disease at the extremes of age.\(^2,6,18,19\) In infants, RSV causes bronchiolitis, pneumonia, tracheobronchitis, and otitis media, while in older adults it can cause pneumonia, as well as exacerbation of chronic obstructive pulmonary disease (COPD) and congestive heart failure (CHF). For healthy older children and young adults, clinical presentation of RSV resembles the common cold, with mild to moderate cough and nasal congestion.

When RSV presents similar to the common cold it is unlikely to cause significant fever, giving patients no signal to self-isolate. If they go to work in day cares, nursing homes, hospitals, and other locations, they may unknowingly spread RSV to others who may be more vulnerable to severe outcomes.

**Risk Factors for More Severe RSV Outcomes with Aging**

Gradual deterioration of the immune system due to aging (immunosenescence) is one of several reasons why older adults are at increased risk from viral respiratory disease.\(^20\) Even the most vital and active older adult will experience some immunosenescence as a consequence of aging, but it is important to note that age alone is not the only determining factor. Frailty, marked by a lack of physiologic reserve,\(^21\) may predict immunosenescence and response to immunization better than age.\(^22,23\)

As adults age, cellular immunity changes include decreased naïve T cells, increased memory T-cell count, decreased T-cell proliferation with Th1 and Th2 imbalances, and increased levels of inflammatory mediators. Older adults also have decreased B-cell responses to new antigens and decreased cytotoxic T-cell activity, resulting in less effective natural killer cells in the immune system.

Anatomically, older adults have decreased strength of the respiratory muscles and diaphragm, which impedes lung expansion. Older adults also have decreased protective mucus levels, lung compliance, and elastin.

**Annual Attack Rate and RSV Mortality in Adults Age 65 Years and Older**

Based on data from a four-year study, the Centers for Disease Control and Prevention (CDC) estimates 14,000 annual deaths caused by RSV in US adults age 65 years and older.\(^9\) A statistical model by Thompson et al.\(^1\) encompassing a 10-year period estimated more than 11,000 annual respiratory and circulatory deaths due to RSV in the US with 78 percent in patients age 65 years
and older. During the surveillance period, RSV was associated with more deaths in this age group than influenza B or the influenza A (H1N1) strain, but fewer deaths than the more severe influenza A (H3N2) strain.

While a hallmark of influenza is its annual seasonal variability, RSV is more consistent in its attack rate and severity. According to a study by Falsey et al, over four winter respiratory seasons in Rochester, NY (1999-2003), RSV infection developed annually in an average of 5.5 percent (range, 3 to 7 percent) of healthy adults age 65 years and older (i.e., without COPD or CHF) and 4 to 10 percent of high-risk adults age 21 years and older (i.e., diagnosed with chronic heart or lung disease). The number of patients with RSV in this study was approximately double the number of patients with influenza, but a high level of influenza vaccination coverage was noted in the study population.

The investigators also evaluated all adults age 65 years and older and those with underlying cardiopulmonary disease at any age who were admitted to a local hospital with a spectrum of acute cardiopulmonary symptoms. RSV and influenza were responsible for 9.6 percent and 10.5 percent of these hospitalizations, respectively. Based on discharge diagnosis, RSV accounted for 10.6 percent of hospitalizations for pneumonia, 11.4 percent for COPD, 7.2 percent for asthma, and 5.4 percent for CHF.

The Cost of RSV in Older Adults

There are limited data on the cost of RSV in adults. A study published in 2000 estimated the annual cost of RSV-related acute respiratory infection in adults age 65 years only at almost $103 million. Based on Social Security Administration estimates of an additional 19 to 21 years life expectancy for individuals reaching age 65 years today, a progressively aging population, and rising healthcare costs, the US price tag for RSV in the age 65 years and older population is likely much greater and may be well into the billions of dollars.

A striking finding in this study was that nearly half of the total cost of RSV was for outpatient oral antibiotics, which would only be medically appropriate for patients with bacterial co-infection. The study by Falsey et al. found that only 10 percent of older and high-risk adults hospitalized with RSV infection had concomitant bacterial infection. In addition to adding to unnecessary costs, overuse of antibiotics is the single most important risk factor leading to antibiotic resistance.

Preventing RSV in people age 65 years and older could reduce both short- and long-term disability and reduce the burden on the US healthcare system, resulting in: fewer acute illnesses and exacerbations of chronic conditions; less contact with healthcare facilities, especially during the winter respiratory season; fewer unnecessary antibiotic prescriptions; and less financial burden.

Clinical Presentation, Diagnosis, and Treatment

RSV and influenza A present with strikingly similar symptoms in adults, making it “nearly impossible,” according to Walsh et al, to distinguish between the two infections based on clinical presentation alone. Nearly all RSV-infected adults (89 percent) exhibit some combination of acute respiratory symptoms (Table 1).

Testing for RSV is not performed routinely in outpatient settings because it is not widely available, it is expensive, and there is no clinical application for the results since there are no
RSV illness usually starts with nasal congestion and rhinorrhea, which progress over several days. Cough, often with sputum production, is common and can be accompanied by dyspnea and wheezing, a hallmark of RSV infection across all ages. On average, patients with RSV present to a doctor or the emergency department on day five to seven of the illness.

There is little difference in RSV and influenza symptoms in adults of any age with high-risk conditions (e.g., chronic heart or lung disease) and otherwise healthy adults age 65 years and older without high-risk conditions (Tables 1 and 2). Healthy adults with RSV tend to report less fever and dyspnea, and more wheezing than adults with influenza. Among hospitalized adults with RSV a substantial proportion report wheezing with both RSV (73 percent) and influenza infection (53 percent).

Absence of fever in patients with RSV appears to be one of the few clues differentiating RSV from influenza. Although patients with RSV and influenza report similar symptoms, albeit with differing frequencies, patients with RSV do not seek medical attention as quickly and experience a longer time from symptom onset to hospitalization.

While the data show a milder course of illness for RSV compared with influenza, it is worth noting that influenza severity can vary substantially by season according to the circulating strain. In the six-year Sundaram study, the first four seasons were marked by either dominant or co-circulation of the influenza A (H3N2) virus, which causes more severe illness than influenza A (H1N1) and B viruses.

Patients hospitalized with RSV have similar outcomes as patients hospitalized with influenza.

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### Table 1: Symptoms in Outpatients with Laboratory-Confirmed RSV vs. Influenza A over Four Seasons, 1999-2003—Rochester, NY

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Healthy, age ≥65 years</th>
<th>High-Risk, age ≥21 years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RSV, % n = 48</td>
<td>Influenza A, % n = 18</td>
</tr>
<tr>
<td>Nasal congestion</td>
<td>83</td>
<td>65</td>
</tr>
<tr>
<td>Cough</td>
<td>79</td>
<td>78</td>
</tr>
<tr>
<td>Sputum production</td>
<td>64</td>
<td>66</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>9</td>
<td>58</td>
</tr>
<tr>
<td>Wheeze</td>
<td>23</td>
<td>50</td>
</tr>
<tr>
<td>Constitutional</td>
<td>53</td>
<td>59</td>
</tr>
<tr>
<td>Fever</td>
<td>18</td>
<td>31</td>
</tr>
</tbody>
</table>

*High risk defined as having physician-diagnosed congestive heart failure or chronic pulmonary disease; †10 percent age <54 years, 17 percent age 55-64 years, 73 percent age ≥65 years. Table compiled by Edward E. Walsh, MD with data from Falsey AR, et al. N Engl J Med. 2005;352(17):1749-1759.

Preventing RSV in adults age 65 years and older could reduce both short- and long-term disability and reduce the burden on the US healthcare system.
In the Falsey study, 28 percent of those hospitalized with RSV died compared to 7 percent for influenza. In a study by Lee et al., 29 percent of those hospitalized with RSV died compared with 10 percent hospitalized with influenza. Patients hospitalized with either influenza or RSV are typically admitted under a wide range of diagnoses, similar across both groups. These include pneumonia (39 to 46 percent), acute exacerbation of COPD (23 to 35 percent), CHF (9 to 13 percent), asthma (7 to 8 percent), bronchitis (1 to 6 percent), and myocardial infarction (1 to 3 percent).

Accurate RSV Diagnosis Relies on Laboratory Testing

Since the clinical syndrome is nonspecific, laboratory testing is required for accurate RSV diagnosis. At the current time, PCR is the diagnostic test of choice with ~85 percent sensitivity in adults. Viral shedding starts soon after infection in adults and peaks at about day three, followed by a two- to three-day plateau and then a steady decline (Figure 2). Nasal shedding can last 10 days or more, making it possible to detect RSV by PCR for at least 10 or more days in the average adult patient. Adults age 65 years and older tend to shed slightly higher titers than younger adults (2.8 ± 1.0 vs. 2.0 ± 1.3 log10 PFU [plaque-forming unit]/mL) and for a longer duration (11.3 ± 5.2 vs. 8.7 ± 4.3 days).

Unfortunately, currently available point-of-care rapid antigen tests, especially those based on enzyme immunoassay, which are widely used for infants, have very poor sensitivity in adults due to the relatively low titer of virus shed in respiratory secretions. Serology is slightly more sensitive than PCR testing for detecting RSV in older adults.
Unfortunately, serologic testing results do not return in a timely manner to help with clinical care. In adults, RSV infection is associated with lower viral loads, making detection difficult, especially by rapid antigen tests and viral culture. It is expected that technological advances will soon provide more rapid and equally sensitive PCR-based point-of-care tests with costs that allow more widespread use. This is critical, as it will be important to accurately test for and diagnose RSV once RSV-specific treatments become available.

**RSV Treatment**

RSV treatment in adults is supportive, including antipyretics, supplemental oxygen, and intravenous fluids as needed. Inhaled or systemic corticosteroids and bronchodilators may be used for elderly patients or patients with preexisting pulmonary conditions (e.g., asthma, COPD) with acute wheezing. As referenced earlier, antibiotics are not indicated for patients with RSV, except in cases of concomitant bacterial infection, which occurs in 10 to 30 percent of RSV infections in hospitalized adults. Bacterial complication rates in outpatients with RSV have not been studied.

**New RSV Prevention Approaches on the Horizon**

The RSV surface F protein mediates the virus entry into the host cell and is the major target for vaccines currently in late-phase clinical trials. The F protein undergoes a conformational change during the fusion process, elongating from its prefusion active version to a nonfunctional postfusion state. This may be important for vaccine development because the prefusion F carries a unique neutralizing epitope that is absent in the postfusion F. Currently, both pre- and postfusion forms of F are being assessed as vaccine candidates.

The F protein is relatively well conserved, unlike the hemagglutinin (HA) on influenza virus or the G (attachment protein) of RSV. F is very stable, with little antigenic change over time. An anti-F monoclonal antibody (palivizumab) is protective when administered prophylactically to premature infants, suggesting that induction of neutralizing antibodies against the F protein by immunization may be protective in adults. The F protein also carries CD8+ T-cell epitopes that may be important in protection from disease severity.

The RSV G glycoprotein mediates virus attachment to respiratory epithelial cells, and also can generate neutralizing antibodies, although they are less frequent than with F immunization. The G glycoprotein has a short central conserved domain but the majority of the protein carries hypervariable domains with a wide range of antigenic diversity. It also determines RSV subtype (A or B), and it is highly glycosylated, which may impair antibody binding to the antigen. Unlike F, the G protein does not contain CD8+ T-cell epitopes. These factors have made the F protein the favored target for vaccine-induced immunity.
RSV Vaccines in Development

More than three dozen RSV vaccines for a range of patient populations are currently in preclinical development and more than a dozen are in clinical trials.\(^9\) Vaccines currently in Phase 1 include gene-based vector, subunit, particle-based, and live-attenuated. Live-attenuated vaccines are of particular interest for use in infants because the evidence to date suggests they do not pose a risk for inducing more severe enhanced respiratory disease in RSV-naïve children, which occurred following use of an inactivated whole virus RSV vaccine given to very young infants in the 1960s.\(^{32}\) There is less concern that an inactivated vaccine could be associated with enhanced disease in adults. Two candidate vaccines for older adults have moved beyond Phase 1 trials.

A Phase 2b randomized, double-blind, placebo-controlled trial is evaluating the efficacy of a vaccine from MedImmune (MEDI7510), a single-dose RSV F antigen with a GLA-SE adjuvant, a toll-like receptor 4 (TLR4) agonist (GLA) in oil and water emulsion (SE), that boosts cellular and humoral immune response for prevention of acute RSV-associated illness in adults age 60 years and older.\(^{33}\) All subjects receive an inactivated influenza vaccine and subjects in the intervention arm also receive 120 µg of the RSV F antigen with adjuvant.

The primary efficacy outcome measure is incidence of acute RSV-associated respiratory illness assessed by clinical symptoms along with PCR confirmation. Efficacy is assessed in Season one, with data available at the end of 2016. In Season two, subjects who received MEDI7510 in the northern hemisphere will be re-randomized to receive MEDI7510 or placebo (all subjects receive influenza vaccine) to assess the safety and immunogenicity of repeat dosing (efficacy is not assessed in Season two). The trial enrolled approximately 1,900 participants in North America, Europe, South Africa, and Chile (subjects with significant ongoing illness were permitted to enroll, subjects with autoimmune disorders and significant immunosuppression were excluded).

In the Phase 1b trial (N = 264) MEDI7510 appeared to be safe and immunogenic with no reports of related serious adverse events; however, at the highest dose of the adjuvant, 54 percent of the subjects reported local pain and tenderness at the injection site, a rate similar to inactivated influenza vaccine.\(^{34,35}\)

A Phase 3 randomized, double-blind, placebo-controlled trial is evaluating the efficacy of a vaccine from Novavax, Inc., a single dose of a recombinant subunit RSV F vaccine at a dose of 135 µg for the prevention of moderate to severe RSV-associated lower respiratory tract disease in adults age 60 years and older.\(^{36}\) The primary efficacy outcome measure is number and percent of subjects with moderate to severe RSV-associated lower respiratory tract disease assessed by clinical symptoms (three or more of the following: cough; new or worsening wheezing; new or increased sputum production; new or worsening dyspnea; and observed tachypnea) along with PCR confirmation. The primary safety outcome measure is number and percent of patients with solicited local and systemic adverse events over one-year post-dosing. This study enrolled close to 12,000 US subjects and is scheduled to be completed in 2016.

The Phase 2 trial of the Novavax vaccine (N = 1,599) randomized subjects to placebo or 135 µg RSV F antigen.\(^{37}\) All subjects received inactivated influenza vaccine. The randomization
was stratified based on age (age 60 to 75 years and age >75 years) and presence of ischemic heart disease or CHF (yes/no). The study is complete but results have not yet been published.

**RSV Therapies in Development**

A 2015 paper from Simões et al,\(^\text{38}\) reported on ongoing challenges and opportunities in development of RSV-specific therapies and pointed out that while the impact of RSV in infants is widely recognized, the misperception that RSV is of little to no consequence in adults has slowed drug development for this age group. Development was delayed for all ages due to lack of adequately sensitive point-of-care diagnostic tests, but this challenge has been overcome in recent years.

A review at ClinicalTrials.gov shows that multiple drugs are currently in Phase 2 trials for treatment and prevention of RSV in adults including monoclonal antibodies and small molecules. Antiviral drugs mainly target the RSV F (fusion) protein. Two Phase 3 trials that are underway are focused on RSV treatment in stem cell and bone marrow transplant patients.

**Preparing for RSV Prevention Possibilities**

Experts at the National Foundation for Infectious Diseases (NFID) roundtable discussed gaps in current knowledge about RSV in older adults, as well as limited awareness of the impact of RSV in older adults among HCPs, public health officials, and the public that must be addressed before prevention strategies including vaccines are available.

Improved surveillance is needed to collect data about the incidence and burden of RSV, including hospitalizations and intensive care unit (ICU) admissions in older adults and in adults with high-risk conditions such as COPD. It will be important to collect comprehensive data that will allow public health experts to stratify risk by age (i.e., by “younger” and “older” seniors) and by underlying condition to help drive the best public health vaccination policy.

The question that will need to be addressed is, “Should RSV vaccination policy be driven by age or other measures of frailty and susceptibility (or both)?” Roundtable experts pointed out the difficulty in implementing recommendations based on identifying high-risk conditions versus the much simpler implementation of age-based recommendations.

It will be essential to gather data on the duration of vaccine protection and the issue of re-immunization. Aligning RSV and influenza vaccination recommendations (i.e., annual vaccination before the start of the winter respiratory season) would simplify implementation in many ways. However, there are practical
considerations, such as how delivery of RSV vaccine will impact delivery of other vaccines targeted for older adults and whether the public will accept two annual immunizations, influenza and RSV. Public health policy must be shaped by what will optimize health outcomes, but will need to take into consideration these practical implementation issues.

Vaccine trials should provide some valuable information on correlates of protection and on the clinical predictors of serious outcomes. More information is needed about the predictors of serious outcomes beyond what is known about CHF, COPD, and compromised immune systems.

Since the use of a new vaccine grading system at the Advisory Committee on Immunization Practices (ACIP), cost-effectiveness will be a consideration for RSV vaccines in development. It will be essential to define the overall impact of vaccination on the burden of RSV illness in older and at-risk adults, and on reducing costly inpatient and ICU stays as well as long-term disability.

Finally, RSV vaccines must be safe and provide adequate protection. Optimally, vaccines will be moderately or highly effective against serious RSV outcomes and provide sustained protection through at least one season.

Successful implementation of a new vaccine will rest on raising HCP awareness levels about RSV and its impact on older adults. It will also depend on educating the public about the benefits of vaccination. The impact of RSV on older adults is all but invisible in a sea of winter respiratory viruses; it will take a concerted effort to raise awareness of this serious threat to the older US adult population. Widespread availability of fast and relative inexpensive RSV diagnostic tests in the clinical setting would help improve awareness.

Once vaccines are licensed and recommended, additional questions will need to be answered, including cost and payment for the vaccine itself and administration (e.g., coverage under Medicare Part B or under the more complex Medicare Part D, private insurance coverage for a vaccine approved for individuals under age 65 years, etc.) Medical practice infrastructure, including seemingly mundane issues such as stocking, storage, and handling, and recording the immunization in state-based immunization registries will also need to be considered and addressed to maximize vaccine uptake.
Summary

Increasing recognition of the considerable burden of RSV illness in older adults (age 65 years and older) coupled with potential new preventions and treatments on the horizon should change the way HCPs focus on RSV now. It is important to build awareness and consensus among public health and immunization communities about the need to protect older adults from RSV infection. This will help ensure that when vaccines and other prevention options become available to protect this population from RSV they are used optimally and according to public health recommendations.

Participants

NFID convened a panel of stakeholders and subject matter experts to examine the burden of RSV in US adults age 65 years and older. The following participated in the June 2016 RSV Roundtable in Atlanta, GA, which served as the basis for this report.

Carole A. Anderson, MEd, EdD
Vice President, Education
American Society on Aging

Edward A. Belongia, MD
Director, Center for Clinical Epidemiology & Population Health
Marshfield Clinic Research Foundation

Arnold S. Monto, MD
Professor, Epidemiology
Thomas Francis Jr. Collegiate Professor of Public Health
University of Michigan School of Public Health

Pedro (Tony) A. Piedra, MD
Professor, Virology and Microbiology
Baylor College of Medicine

L. Michael Posey, BS Pharm, MA
Editor, National Adult Vaccination Program Immunizations Newsletter
The Gerontological Society of America

Pamela G. Rockwell, DO
Associate Professor, Family Medicine
University of Michigan Medical School
Medical Director, Family Medicine at Domino’s Farms
American Academy of Family Physicians

William Schaffner, MD
Medical Director, National Foundation for Infectious Diseases
Professor of Preventive Medicine and Infectious Diseases
Vanderbilt University School of Medicine

H. Keipp Talbot, MD, MPH
Assistant Professor, Division of Infectious Diseases
Vanderbilt University School of Medicine

Edward E. Walsh, MD
Professor of Medicine
University of Rochester Medical Center

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References


35. Villafana TL, Falloon J, Griffin P. RSV prophylaxis for at risk populations. The Macrae Foundation’s XVIII International Symposium on Respiratory Viral Infections; March 31-April 2, 2016; Lisbon, Portugal.


RSV: A Hidden Annual Epidemic

Respiratory syncytial virus (RSV) is a common cause of serious respiratory illness in adults age 65 years and older but is largely unrecognized even in the medical community.

**Annual Burden:** US adults age 65 years and older

- **14,000** deaths
- **177,000** hospitalizations
- **5.5%** attack rate resulting in **2.6 million** cases each year

**Transmission:**

- Circulates seasonally along with many winter respiratory viruses
- Most infections occur between November and May in the US

**Spreads Easily, Reinfection Common**

- **2 in 3** adults will get reinfected within 8 months

**Symptoms:**

- Often misdiagnosed as flu...
- Nasal congestion and runny nose
- Cough
- Shortness of breath and wheezing
- Fever

**Who Is At Risk**

- **65+ Years Old**
- Other Conditions
- The worst outcomes (hospitalization, death) are in older adults and those with high-risk conditions (e.g., heart or lung disease)

To learn more, visit www.nfid.org/rsv