HHS Public Access

Author manuscript

Clin Chest Med. Author manuscript; available in PMC 2018 March 09.

Published in final edited form as:

Clin Chest Med. 2017 March ; 38(1): 29–36. doi:10.1016/j.ccm.2016.11.010.

Respiratory Syncytial Virus infection: an illness for all ages

Edward E. Walsh, M.D.

Professor of Medicine, Infectious Diseases Division, University of Rochester School of Medicine, Department of Medicine, Rochester General Hospital

Synopsis

RSV is the single most important cause of severe respiratory infection in very young infants. It has also been recently recognized as a significant cause of severe illness in elderly adults and those with underlying cardiopulmonary disease and the immunocompromised. RSV is also suspected of playing a major role in the development of asthma. Prophylaxis in high-risk infants using a monoclonal antibody is the only effective specific therapy available at this time but recent breakthroughs in vaccine design and antiviral drugs offer the promise of effective prophylactic and therapeutic agents for RSV.

Keywords

Respiratory Syncytial Virus; Bronchiolitis; Chronic Obstructive Pulmonary Disease; Antivirals; Asthma; Vaccines; Adults

Respiratory Syncytial Virus (RSV) was first identified in 1956 by Robert Chanock is currently recognized as the most important cause of severe respiratory illness in infants and young children, clinically manifest most often as bronchiolitis. (1) The virus has also more recently been identified as a significant contributor to morbidity and mortality in older adults and severely immunocompromised persons. (2)

Virus structure and genome

RSV is an enveloped negative sense, single-strand RNA virus classified in the family *Pneumoviridae* along with human metapneumovirus, another cause of respiratory infections. The RSV genome contains 10 distinct genes that encode 11 individual proteins, each with distinct roles in viral infection and immune evasion (figure 1). (3) Surface glycoproteins protruding from the envelope include the viral attachment protein (G) and the fusion protein (F) that mediates entry of the viral genome into cells while transitioning from a thermolabile prefusion F to a stable post-fusion F. G may play a role in modulation of the immune and inflammatory response to infection through its CX3C chemokine homologue that binds the

Contact: Edward E Walsh M.D., Infectious Diseases Unit, Rochester General Hospital, 1425 Portland Avenue, Rochester, New York 14621, Phone: 585-922-4331, Fax: 585-922-5168, Edward.walsh@rochesterregional.org.

CX3C receptor (CX3CR) on immune cells and primary ciliated respiratory epithelial cell. (4, 5) Two nonstructural RSV proteins (NS1 and NS2) inhibit cellular antiviral innate type I interferons providing defense against the host immune response.

There are two major viral groups, designated A and B, each with numerous subgroups, best identified by G gene sequence variation. (6) However, a causal relationship between antigenic variation in G and reinfections has not been firmly established. Antibody to F and the G proteins is considered a primary determinant of immunity.

Epidemiology

In the temperate climates annual epidemics occur during the winters. In the US epidemics generally begin in the southeast in late summer and spread north and westward reaching a peak in January and February in the northeast and Pacific Northwest. (7) RSV circulation generally persists for 16–22 weeks in a community, and overlaps with the more sharply defined 6–8 week influenza epidemics. In the tropics RSV circulation is more variable, frequently being more common during the rainy season, and circulating throughout the year. (8) Group A and B RSV viruses co-circulate, with group A viruses tending to be more frequent.

Older children commonly introduce the virus into the family with spread to infants and parents. (9) RSV is most effectively transmitted by large fomites (nasal secretions) while aerosol is less important. The virus is stable for several hours on hard surfaces and hands, allowing transmission by direct contact with contaminated objects. The introduction of strict infection control policies in hospital settings (isolation and hand washing) and personal protective equipment (gowns, gloves and possibly goggles) reduced nosocomial transmission. (10)

Pediatric RSV infection

The importance of RSV on the health of infants and young children cannot be underestimated, causing acute illness and, importantly, may be causally related to the development of subsequent wheezing in childhood and asthma later in life. Fifty to 70% of newborn infants become infected during their first winter, with virtually all by age two. Reinfections with RSV continue throughout childhood although their severity diminishes. In the US, approximately 1–2% of infants in their first year of life are hospitalized with RSV infection, while another 20% will be seen in pediatric offices or emergency rooms for acute respiratory symptoms. (11) Pediatric mortality from RSV in developed countries is low (~ 50–100 annually in the US), however, in the developing world RSV is estimated to result in 66,000–199,000 deaths and >3 million hospitalizations in children under age 5 years. (12, 13)

The course of RSV illness and its manifestations follow a similar pattern in most infants although disease severity is highly variable. Following an incubation period of 4–6 days, nasal congestion with mucus discharge and fever are followed by cough, tachypnea and respiratory distress with chest retractions and wheezing, the hallmark of bronchiolitis. In young preterm infants, apnea will occasionally be an early manifestation of RSV. The

clinical picture of RSV in young infants can change during observation, with hypoxia and physical findings fluctuating even in a matter of several minutes. Radiographic reveal air trapping and infiltrates related to obstructive atelectasis or vial pneumonia. This variability in the clinical appearance of an infant with RSV can make decisions about further observation or to hospitalize difficult.

Bacterial co-infection with *Streptococcus pneumoniae* or *Hemophilus influenzae*, either as otitis media or pneumonia, can complicate RSV infection although the precise relationship of the interaction, incidence and significance of bacteria in respiratory secretions is not firmly established. A review of 2396 infants and children admitted with RSV bronchiolitis noted bacterial infection uncommon (1.6%). (14) However, in a UK study 42% of lower airway secretions had pathogenic bacteria in mechanically ventilated infants and 21.8% were considered to have bacterial co-infection. (15) A recent study of the nasal microbiome of RSV infected infants found that abundance of *S. pneumoniae* and *H. influenzae*, but not *Staphylococcus aureus,* was associated with changes in the host immune response as measured by gene expression of peripheral blood mononuclear cells. (16) Finally, studies from the US and South Africa reported 18% and 32% reductions, respectively, in RSV-confirmed hospitalization following introduction of conjugate pneumococcal vaccine. (17–19)

Many risk factors associated with severe disease including gestational age < 29 weeks, chronic lung disease and cyanotic heart disease most important.(1) The incidence of hospitalization among preterm infants with chronic lung disease was 12.8% in one study. (20) Nevertheless, ~70% of hospitalized infants are full term previously healthy infants. Although lack of breast feeding, exposure to environmental tobacco smoke, crowding, day care attendance and lower socio-economic status have been associated with risk of severe disease, a recent population based surveillance study of 2539 hospitalizations among 32,000 infants found only young chronological age associated with increased hospitalization rates in full term infants, with the peak rate in 0–5 month olds. (11, 21)

Laboratory diagnosis is often sought in hospitalized infants as several other respiratory viruses, especially human metapneumovirus, can also manifest as classic bronchiolitis. A specific diagnosis allows proper institution of appropriate infection prevention measures. Nucleic acid detection tests using reverse transcriptase-polymerase chair reaction (RT-PCR) are considered the gold standard while rapid antigen tests having a sensitivity of ~70% compared to RT-PCR. (22) Viral titers are highest on admission, peak at day three of illness with shedding typically lasting 11 days (23–25)

Treatment is primarily supportive, primarily oxygen for SaO2 <90, and despite numerous large multicenter randomized trials, no specific therapy has been found to consistently lessen severity or shorten the natural course of the illness. (1) Inhaled ribavirin is licensed for treatment of RSV infection in infants based on early studies demonstrating modest benefit, but is not recommended for most hospitalized infants.

Prophylaxis with palivizumab (SynagisR), a humanized murine monoclonal antibody directed at a neutralizing epitope on the post-fusion F protein is licensed for specific groups

of infants. (20) Current recommendations by the American Academy of Pediatrics advise giving up to 5 monthly injections to premature infants <29 weeks gestation during their first winter and for infants < 32 weeks gestation with chronic lung disease of prematurity who required supplemental oxygen, and children with acyanotic congenital heart disease. Treatment of established infection with monoclonal antibody has not been associated with clinical benefit despite a reduction in viral load in severely ill intubated infants. (26)

Long-term sequelae of RSV infection is a topic of great interest and controversy specifically with regards to the development of asthma. (27) Following RSV infection, many infants will develop wheezing with other viral infections, a situation that tends to abate by age seven. However, children with severe RSV bronchiolitis early in life have been shown to have a higher risk of developing childhood asthma and a greater incidence of asthma in young adulthood and greater deficits in peak airway flow if they are smokers. (28) It has been postulated that severe RSV in infancy may also predisposed to the development of COPD later in life. (29) However, it is still unclear if these sequelae are causally related to RSV infection or are simply reflections of a genetic predisposition to airway obstruction during any viral infection of antigenic stimulation. (1, 27)

Adult RSV infection

Although RSV in adults was described shortly after its identification in 1956 the impact and burden of RSV in this population was not appreciated until recently. As noted above, immunity to RSV is incomplete and thus reinfection is common despite relatively high levels of serum neutralizing antibodies in adults. Nevertheless, reinfection with RSV and disease severity has been associated with lower levels of serum neutralizing antibody and nasal IgA (30). RSV infects adults at any age although severe illness occurs primarily in elderly persons, especially those with underlying cardiopulmonary disease or those who are frail. It is postulated that waning cell-mediated immunity plays a role in susceptibility in this age group. (31) Importantly, immunocompromised adults, especially haematopoetic stem cell transplant (HSCT) recipients, those undergoing intensive chemotherapy, and lung transplant patients are at serious risk of severe RSV infection. (32)

The burden of RSV in adults has been determined in a combination of population based prospective surveillance studies, analysis of acute illness presenting for medical care, and by modeling of large medical databases. In prospective surveillance studies in healthy elderly adults and high-risk adults with underlying cardiopulmonary disease the annual winter-time RSV attack rate ranged from 3–7% and 2–10%, respectively. (2, 33) In a 3-year study of acute respiratory illnesses seen by general practitioners in the UK, 19% of 45–64 year olds and 15% of those ≥ 65 years old were diagnosed with RSV. (34) In a recent retrospective analysis of respiratory samples from 2225 subjects with medically attended acute respiratory illness (MAARI) in Marshfield, Wisconsin RSV was identified in 8.2% of those 50–64 years old, 10.2% of those 65–79 and 10.5% of those ≥ 80 years old. (35)

The incidence of RSV among hospitalized adults during the winter season ranges from 6 to 10% in various studies. (2, 35–37) Statistical modeling studies from several countries using large clinical databases coupled with laboratory viral diagnostic data calculated the

morbidity and mortality of RSV in adults to be 12–80% (average 43%) of the concurrently measured impact of influenza (table 1). (12, 38–44)

Clinical findings in adults are variable, being dependent on age, but more significantly on the presence of underlying medical conditions. Infection often begins with typical upper respiratory symptoms but fever is often absent or low grade, and significantly less than in influenza. (2, 35) Illness progresses more slowly than influenza, and patients present for medical care between 4–7 days after symptom onset. As in infants, wheezing is often noted. (45) Constitutional symptoms are less frequent than with influenza, with fever occurring in only 28%. In a study of adults over age 50 with RSV associated MAARI, 61% had fever and 67% wheezed.(35) In three large studies of hospitalized adults with RSV, ~80% had a high-risk medical condition with underlying COPD present in 58–68%.(2, 36, 37) In these studies mortality rates were 6.5–10%. In a prospective surveillance study of a high-risk cohort, of whom 65% had COPD, RSV infection resulted in office visits in 60% and 20% were hospitalized. (2) Radiographic abnormalities are common in adults hospitalized with RSV, with consolidation or ground glass infiltrates in 31–49%. (2, 37)

Immunocompromised individuals have the highest morbidity and mortality from RSV. (32, 46) Upper respiratory symptoms give way to lower respiratory involvement in 30–40% of infected persons around day 7 of illness. High-dose total body irradiation and total lymphocyte count <100/mm, but not serum neutralizing antibody levels or corticosteroid use, were associated with progression from upper to lower tract disease. (47)

Since the attack rate in adults during the RSV season is relatively low and the clinical syndrome non-specific, laboratory confirmation of RSV is critical to accurate diagnosis. RT-PCR is most sensitive (~80%) while virus culture (33%) and rapid enzyme linked antigen detection tests (10%) have poor sensitivity even in HCST patients. (2, 48, 49) Sputum RT-PCR testing can also increase yield by 22%.(50) The mean duration of RSV shedding in adults is ~10 days with mean nasal secretion titers of 2.0–2.8 $\log_{10}$ per ml with higher titers and longer shedding noted in older patients and in those with more severe illness. (51–53)

Management of adults with RSV infection is supportive. The use of antibiotics is common among both outpatients and inpatients with RSV, even when the chest radiograph is clear.(2, 37) The precise incidence of bacterial co-infection during RSV associated hospitalization has not been extensively studied but is reported to be 12–15%.(2, 37) In a comprehensive analysis of hospitalized adults with viral infections, 31% of RSV infected persons had evidence of invasive bacterial infection based on either standard tests or a high serum procalcitonin. (54) Use of ribavirin (aerosolized, oral or intravenously) is not recommended in adults with the exception of severely immunocompromised persons in whom early ribavirin treatment, often coupled with immune globulin, was the most significant factor in reducing mortality.(46)

Future vaccine and antiviral prospects for RSV

Currently there are no licensed vaccines for prevention in any age group. As of September 2016 there are over 40 vaccines in preclinical development and more than 15 in various

clinical phases of study. Vaccine approaches include live attenuated vaccines, vectored vaccines expressing protective RSV antigens, inactivated subunit vaccines (primarily pre-fusion or post-fusion forms of F) with and without novel adjuvants, DNA based vaccines and newer monoclonal antibodies with a prolonged half-life (see www.path.org). Live attenuated vaccines developed using reverse genetics are currently in clinical trials in young infants. (55) Subunit vaccines are being developed for use in adults, including maternal immunization during late pregnancy to protect infants from RSV infection early in life by increasing placental transport of neutralizing antibody to the newborn. These studies are currently in phase 2 studies. A new development in the evolution of subunit and vectored vaccines is the recognition that the prefusion form of F protein carries potent neutralizing epitopes not found in the post-fusion F that has been studied in several prior vaccine trials. (3)

Several new small molecule antivirals have also entered early phase 1 and 2 clinical trials in pediatric and adult age groups, including immunocompromised persons. They include a fusion inhibitor with a half-life that allows a single dose and a nucleoside analogue that inhibits the RSV polymerase. (56, 57) Both of these drugs can be administered orally, and have been demonstrated to have good safety profiles and antiviral and clinical efficacy in a human challenge model of RSV infection. Finally, as noted above there are two new long half-life monoclonal antibodies currently being evaluated for prophylaxis in high-risk infants.(58)

References

1. Meissner HC. Viral Bronchiolitis in Children. N Engl J Med. 2016 Jan 7; 374(1):62–72. [PubMed: 26735994]
2. Falsey AR, Hennessey PA, Formica MA, Cox C, Walsh EE. Respiratory syncytial virus infection in elderly and high-risk adults. N Engl J Med. 2005 Apr 28; 352(17):1749–59. [PubMed: 15858184]
3. Graham BS, Modjarrad K, McLellan JS. Novel antigens for RSV vaccines. Curr Opin Immunol. 2015 Aug.35:30–8. [PubMed: 26070108]
4. Johnson SM, McNally BA, Ioannidis I, Flano E, Teng MN, Oomens AG, et al. Respiratory Syncytial Virus Uses CX3CR1 as a Receptor on Primary Human Airway Epithelial Cultures. PLoS Pathog. 2015 Dec 11.11(12):e1005318. [PubMed: 26658574]
5. Chirkova T, Boyoglu-Barnum S, Gaston KA, Malik FM, Trau SP, Oomens AG, et al. Respiratory syncytial virus G protein CX3C motif impairs human airway epithelial and immune cell responses. J Virol. 2013 Dec; 87(24):13466–79. [PubMed: 24089561]
6. Bose ME, He J, Shrivastava S, Nelson MI, Bera J, Halpin RA, et al. Sequencing and analysis of globally obtained human respiratory syncytial virus A and B genomes. PLoS One. 2015 Mar 20.10(3):e0120098. [PubMed: 25793751]
7. Panozzo CA, Fowlkes AL, Anderson LJ. Variation in timing of respiratory syncytial virus outbreaks: lessons from national surveillance. Pediatr Infect Dis J. 2007 Nov; 26(11 Suppl):S41–5. [PubMed: 18090199]
8. Bloom-Feshbach K, Alonso WJ, Charu V, Tamerius J, Simonsen L, Miller MA, et al. Latitudinal variations in seasonal activity of influenza and respiratory syncytial virus (RSV): a global comparative review. PLoS One. 2013; 8(2):e54445. [PubMed: 23457451]
9. Hall CB, Geiman JM, Biggar R, Kotok DI, Hogan PM, Douglas GR Jr. Respiratory syncytial virus infections within families. N Engl J Med. 1976 Feb 19; 294(8):414–9. [PubMed: 173995]
10. French CE, McKenzie BC, Coope C, Rajanaidu S, Paranthaman K, Pebody R, et al. Risk of nosocomial respiratory syncytial virus infection and effectiveness of control measures to prevent

transmission events: a systematic review. Influenza Other Respir Viruses. 2016 Jul; 10(4):268–90. [PubMed: 26901358]

11. Hall CB, Weinberg GA, Iwane MK, Blumkin AK, Edwards KM, Staat MA, et al. The burden of respiratory syncytial virus infection in young children. N Engl J Med. 2009 Feb 5; 360(6):588–98. [PubMed: 19196675]
12. Zhou H, Thompson WW, Viboud CG, Ringholz CM, Cheng PY, Steiner C, et al. Hospitalizations associated with influenza and respiratory syncytial virus in the United States, 1993–2008. Clin Infect Dis. 2012 May; 54(10):1427–36. [PubMed: 22495079]
13. Nair H, Nokes DJ, Gessner BD, Dherani M, Madhi SA, Singleton RJ, et al. Global burden of acute lower respiratory infections due to respiratory syncytial virus in young children: a systematic review and meta-analysis. Lancet. 2010 May 1; 375(9725):1545–55. [PubMed: 20399493]
14. Purcell K, Fergie J. Concurrent serious bacterial infections in 2396 infants and children hospitalized with respiratory syncytial virus lower respiratory tract infections. Arch Pediatr Adolesc Med. 2002 Apr; 156(4):322–4. [PubMed: 11929363]
15. Thorburn K, Harigopal S, Reddy V, Taylor N, van Saene HK. High incidence of pulmonary bacterial co-infection in children with severe respiratory syncytial virus (RSV) bronchiolitis. Thorax. 2006 Jul; 61(7):611–5. [PubMed: 16537670]
16. de Steenhuijsen Piters WA, Heinonen S, Hasrat R, Bunsow E, Smith B, Suarez-Arrabal MC, et al. Nasopharyngeal Microbiota, Host Transcriptome and Disease Severity in Children with Respiratory Syncytial Virus Infection. Am J Respir Crit Care Med. 2016 May 2.
17. Weinberger DM, Klugman KP, Steiner CA, Simonsen L, Viboud C. Association between respiratory syncytial virus activity and pneumococcal disease in infants: a time series analysis of US hospitalization data. PLoS Med. 2015 Jan 6.12(1):e1001776. [PubMed: 25562317]
18. Madhi SA, Klugman KP. Vaccine Trialist Group. A role for Streptococcus pneumoniae in virus-associated pneumonia. Nat Med. 2004 Aug; 10(8):811–3. [PubMed: 15247911]
19. Madhi SA, Kuwanda L, Cutland C, Klugman KP. Five-year cohort study of hospitalization for respiratory syncytial virus associated lower respiratory tract infection in African children. J Clin Virol. 2006 Jul; 36(3):215–21. [PubMed: 16678480]
20. American Academy of Pediatrics Committee on Infectious Diseases, American Academy of Pediatrics Bronchiolitis Guidelines Committee. Updated guidance for palivizumab prophylaxis among infants and young children at increased risk of hospitalization for respiratory syncytial virus infection. Pediatrics. 2014 Aug; 134(2):e620–38. [PubMed: 25070304]
21. Hall CB, Weinberg GA, Blumkin AK, Edwards KM, Staat MA, Schultz AF, et al. Respiratory syncytial virus-associated hospitalizations among children less than 24 months of age. Pediatrics. 2013 Aug; 132(2):e341–8. [PubMed: 23878043]
22. Chartrand C, Tremblay N, Renaud C, Papenburg J. Diagnostic Accuracy of Rapid Antigen Detection Tests for Respiratory Syncytial Virus Infection: Systematic Review and Meta-analysis. J Clin Microbiol. 2015 Dec; 53(12):3738–49. [PubMed: 26354816]
23. DeVincenzo JP, El Saleeby CM, Bush AJ. Respiratory syncytial virus load predicts disease severity in previously healthy infants. J Infect Dis. 2005 Jun 1; 191(11):1861–8. [PubMed: 15871119]
24. El Saleeby CM, Bush AJ, Harrison LM, Aitken JA, Devincenzo JP. Respiratory syncytial virus load, viral dynamics, and disease severity in previously healthy naturally infected children. J Infect Dis. 2011 Oct 1; 204(7):996–1002. [PubMed: 21881113]
25. Munywoki PK, Koech DC, Agoti CN, Kibirige N, Kipkoech J, Cane PA, et al. Influence of age, severity of infection, and co-infection on the duration of respiratory syncytial virus (RSV) shedding. Epidemiol Infect. 2015 Mar; 143(4):804–12. [PubMed: 24901443]
26. Malley R, DeVincenzo J, Ramilo O, Dennehy PH, Meissner HC, Gruber WC, et al. Reduction of respiratory syncytial virus (RSV) in tracheal aspirates in intubated infants by use of humanized monoclonal antibody to RSV F protein. J Infect Dis. 1998; 178(6):1555–61. 32676. [PubMed: 9815203]
27. Feldman AS, He Y, Moore ML, Hershenson MB, Hartert TV. Toward primary prevention of asthma. Reviewing the evidence for early-life respiratory viral infections as modifiable risk factors to prevent childhood asthma. Am J Respir Crit Care Med. 2015 Jan 1; 191(1):34–44. [PubMed: 25369458]

28. Voraphani N, Stern DA, Wright AL, Guerra S, Morgan WJ, Martinez FD. Risk of current asthma among adult smokers with respiratory syncytial virus illnesses in early life. Am J Respir Crit Care Med. 2014 Aug 15; 190(4):392–8. [PubMed: 24927374]
29. Martinez FD. Early-Life Origins of Chronic Obstructive Pulmonary Disease. N Engl J Med. 2016 Sep 1; 375(9):871–8. [PubMed: 27579637]
30. Walsh EE, Falsey AR. Humoral and mucosal immunity in protection from natural respiratory syncytial virus infection in adults. J Infect Dis. 2004 Jul 15; 190(2):373–8. [PubMed: 15216475]
31. Malloy AM, Falsey AR, Ruckwardt TJ. Consequences of immature and senescent immune responses for infection with respiratory syncytial virus. Curr Top Microbiol Immunol. 2013; 372:211–31. [PubMed: 24362692]
32. Chemaly RF, Shah DP, Boeckh MJ. Management of respiratory viral infections in hematopoietic cell transplant recipients and patients with hematologic malignancies. Clin Infect Dis. 2014 Nov 15; 59(Suppl 5):S344–51. [PubMed: 25352629]
33. Falsey AR, Walsh EE, Capellan J, Gravenstein S, Zambon M, Yau E, et al. Comparison of the safety and immunogenicity of 2 respiratory syncytial virus (rsv) vaccines--nonadjuvanted vaccine or vaccine adjuvanted with alum--given concomitantly with influenza vaccine to high-risk elderly individuals. J Infect Dis. 2008 Nov 1; 198(9):1317–26. [PubMed: 18855558]
34. Zambon MC, Stockton JD, Clewley JP, Fleming DM. Contribution of influenza and respiratory syncytial virus to community cases of influenza-like illness: an observational study. Lancet. 2001; 358:1410–6. 32676. [PubMed: 11705487]
35. Sundaram ME, Meece JK, Sifakis F, Gasser RA Jr, Belongia EA. Medically attended respiratory syncytial virus infections in adults aged >/= 50 years: clinical characteristics and outcomes. Clin Infect Dis. 2014 Feb; 58(3):342–9. [PubMed: 24265361]
36. Widmer K, Griffin MR, Zhu Y, Williams JV, Talbot HK. Respiratory syncytial virus- and human metapneumovirus-associated emergency department and hospital burden in adults. Influenza Other Respir Viruses. 2014 May; 8(3):347–52. [PubMed: 24512531]
37. Lee N, Lui GC, Wong KT, Li TC, Tse EC, Chan JY, et al. High morbidity and mortality in adults hospitalized for respiratory syncytial virus infections. Clin Infect Dis. 2013 Oct; 57(8):1069–77. [PubMed: 23876395]
38. Mullooly JP, Bridges CB, Thompson WW, Chen J, Weintraub E, Jackson LA, et al. Influenza-and RSV-associated hospitalizations among adults. Vaccine. 2007 Jan 15; 25(5):846–55. [PubMed: 17074423]
39. Thompson WW, Shay DK, Weintraub E, Brammer L, Cox N, Anderson LJ, et al. Mortality associated with influenza and respiratory syncytial virus in the United States. JAMA. 2003 Jan 8; 289(2):179–86. [PubMed: 12517228]
40. van Asten L, van den Wijngaard C, van Pelt W, van de Kassteele J, Meijer A, van der Hoek W, et al. Mortality attributable to 9 common infections: significant effect of influenza A, respiratory syncytial virus, influenza B, norovirus, and parainfluenza in elderly persons. J Infect Dis. 2012 Sep 1; 206(5):628–39. [PubMed: 22723641]
41. Fleming DM, Taylor RJ, Lustig RL, Schuck-Paim C, Haguinet F, Webb DJ, et al. Modelling estimates of the burden of Respiratory Syncytial virus infection in adults and the elderly in the United Kingdom. BMC Infect Dis. 2015 Oct 23.15 443,015–1218-z.
42. Matias G, Taylor R, Haguinet F, Schuck-Paim C, Lustig R, Shinde V. Estimates of mortality attributable to influenza and RSV in the United States during 1997–2009 by influenza type or subtype, age, cause of death, and risk status. Influenza Other Respir Viruses. 2014 Sep; 8(5):507–15. [PubMed: 24975705]
43. Chan PK, Tam WW, Lee TC, Hon KL, Lee N, Chan MC, et al. Hospitalization Incidence, Mortality, and Seasonality of Common Respiratory Viruses Over a Period of 15 Years in a Developed Subtropical City. Medicine (Baltimore). 2015 Nov.94(46):e2024. [PubMed: 26579810]
44. Goldstein E, Greene SK, Olson DR, Hanage WP, Lipsitch M. Estimating the hospitalization burden associated with influenza and respiratory syncytial virus in New York City, 2003–2011. Influenza Other Respir Viruses. 2015 Sep; 9(5):225–33. [PubMed: 25980600]
45. Hall CB, Long CE, Schnabel KC. Respiratory syncytial virus infections in previously healthy working adults. Clin Infect Dis. 2001 Sep 15; 33(6):792–6. [PubMed: 11512084]

46. Shah DP, Ghantoji SS, Shah JN, El Taoum KK, Jiang Y, Popat U, et al. Impact of aerosolized ribavirin on mortality in 280 allogeneic haematopoietic stem cell transplant recipients with respiratory syncytial virus infections. J Antimicrob Chemother. 2013 Apr 9.
47. Kim YJ, Guthrie KA, Waghmare A, Walsh EE, Falsey AR, Kuypers J, et al. Respiratory syncytial virus in hematopoietic cell transplant recipients: factors determining progression to lower respiratory tract disease. J Infect Dis. 2014 Apr 15; 209(8):1195–204. [PubMed: 24368837]
48. Casiano-Colon AE, Hulbert BB, Mayer TK, Walsh EE, Falsey AR. Lack of sensitivity of rapid antigen tests for the diagnosis of respiratory syncytial virus infection in adults. J Clin Virol. 2003 Oct; 28(2):169–74. [PubMed: 12957187]
49. Englund JA, Piedra P, Jewell A, Baxter BB, Whimbey E, Patel K. Rapid diagnosis of respiratory syncytial virus infections in immunocompromised adults. J Clin Microbiol. 1996; 34(7):1649–53. [PubMed: 8784563]
50. Branche AR, Walsh EE, Formica MA, Falsey AR. Detection of respiratory viruses in sputum from adults by use of automated multiplex PCR. J Clin Microbiol. 2014 Oct; 52(10):3590–6. [PubMed: 25056335]
51. Walsh EE, Peterson DR, Kalkanoglu AE, Lee FE, Falsey AR. Viral shedding and immune responses to respiratory syncytial virus infection in older adults. J Infect Dis. 2013 May; 207(9): 1424–32. [PubMed: 23382572]
52. Duncan CB, Walsh EE, Peterson DR, Lee FE, Falsey AR. Risk factors for respiratory failure associated with respiratory syncytial virus infection in adults. J Infect Dis. 2009 Oct 15; 200(8): 1242–6. [PubMed: 19758094]
53. Lee N, Chan MC, Lui GC, Li R, Wong RY, Yung IM, et al. High Viral Load and Respiratory Failure in Adults Hospitalized for Respiratory Syncytial Virus Infections. J Infect Dis. 2015 Oct 15; 212(8):1237–40. [PubMed: 25904604]
54. Falsey AR, Becker KL, Swinburne AJ, Nylen ES, Formica MA, Hennessey PA, et al. Bacterial complications of respiratory tract viral illness: a comprehensive evaluation. J Infect Dis. 2013 Aug 1; 208(3):432–41. [PubMed: 23661797]
55. Karron RA, Buchholz UJ, Collins PL. Live-attenuated respiratory syncytial virus vaccines. Curr Top Microbiol Immunol. 2013; 372:259–84. [PubMed: 24362694]
56. DeVincenzo JP, McClure MW, Symons JA, Fathi H, Westland C, Chanda S, et al. Activity of Oral ALS-008176 in a Respiratory Syncytial Virus Challenge Study. N Engl J Med. 2015 Nov 19; 373(21):2048–58. [PubMed: 26580997]
57. DeVincenzo JP, Whitley RJ, Mackman RL, Scaglioni-Weinlich C, Harrison L, Farrell E, et al. Oral GS-5806 activity in a respiratory syncytial virus challenge study. N Engl J Med. 2014 Aug 21; 371(8):711–22. [PubMed: 25140957]
58. Mejias A, Garcia-Maurino C, Rodriguez-Fernandez R, Peeples ME, Ramilo O. Development and clinical applications of novel antibodies for prevention and treatment of respiratory syncytial virus infection. Vaccine. 2016 Sep 27.
59. Graham BS, Modjarrad K, McLellan JS. Novel antigens for RSV vaccines. Curr Opin Immunol. 2015 Aug.35:30–8. [PubMed: 26070108]

Key Points

- RSV is an important respiratory pathogen at both ends of the age spectrum with ~ 100,000 hospitalizations in infants and ~ 177,000 in adults. However, general awareness of RSV in adults among internists and general practitioners is lacking.
- The interaction of RSV with pathogenic bacteria, specifically *S. pneumoniae* and *H. influenzae*, appear to influence disease severity and contribute to morbidity especially in the developing world.
- Prophylaxis with Palivizumab provides effective prevention in specific high-risk infants, but there are currently no effective specific therapies or vaccines for the majority of susceptible infants and adults.

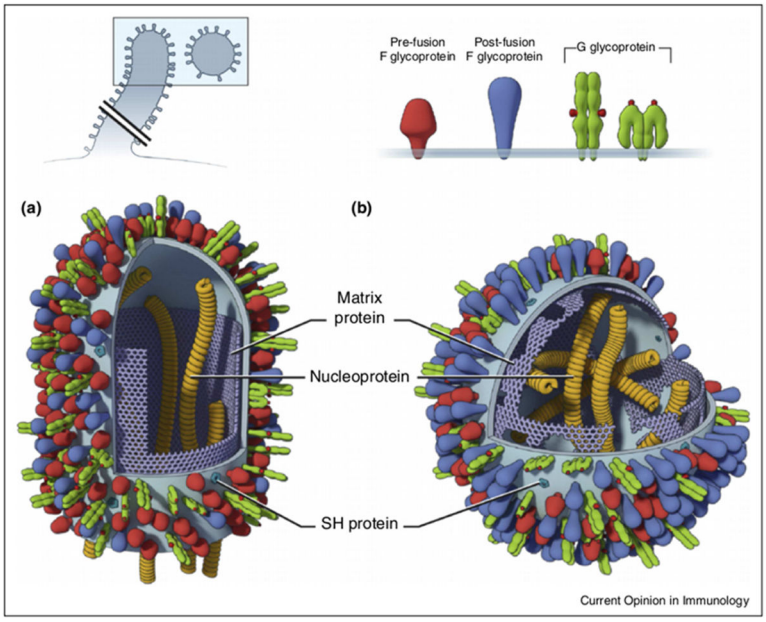

Figure 1.

Schematic depiction of the filamentous and spherical forms of Respiratory Syncytial Virus, indicating the pre- and post-fusion forms of F and the G glycoprotein.

From Graham BS, Modjarrad K, McLellan JS. Novel antigens for RSV vaccines. Curr Opin Immunol. 2015 Aug;35:30–8

Table 1

Summary of epidemiologic modeling studies comparing mortality and hospitalization rates for RSV and influenza in adults age 65 years and above.

Author (reference)	location	Dates (# years)	Outcome Measure	Results
Thompson(39)	US	1990–1999 (9)	Respiratory & Circulatory deaths per 100,000	RSV 26.5 Flu A+B 98.5
Mullooly(38)	Portland, OR	1996–2000 (4)	Annual Pneumonia & Influenza * hospitalization per 10,000	RSV 23.4 Flu 55.6
Zhou(12)	US	1993–2008 (15)	Annual Hospitalizations per 100,000	RSV 86.1 Flu 309
van Asten(40)	Netherlands	1999–2007 (8)	Total Deaths	RSV 13902 Flu A + B 21635
Matias(42)	US	1997–2009 (12)	Annual Deaths from respiratory illness	RSV 9673 Flu 16505
Fleming(41)	UK	1995–2009 (14)	Annual hospitalizations (ratio of RSV:Flu)	RSV 14039 (0.8)
Chan(43)	Hong Kong	1998–2012 (15)	Annual hospitalizations per 10,000	RSV 5.2 (M) 6.1 (F) ** Flu A 19.5 (M) 17.3 (F)
Goldstein(44)	New York City	2003–2011 (9)	Annual hospitalizations per 100,000	RSV 15.3 Flu 125.8

* Influenza unvaccinated high-risk individuals

** M, male; F, female

Table 2

Symptoms in Outpatients with Laboratory-Confirmed RSV vs. Influenza A over Four Seasons, 1999–2003 in Rochester, NY

Symptom	Healthy, age ≥65 years		High-Risk*, age ≥21 years†	
	RSV n=48	Influenza A (%) n=18	RSV (%) n=54	Influenza A (%) n=16
Nasal congestion	83%	83%	65%	79%
Cough	79%	83%	78%	87%
Sputum production	64%	61%	66%	80%
Dyspnea	9%	28%	58%	71%
Wheeze	23%	17%	50%	50%
Constitutional	53%	72%	59%	71%
Fever	18%	44%	31%	47%

*High-risk defined as having physician-diagnosed congestive-heart failure or chronic pulmonary disease;

†10% age <54 years, 17% age 55–64 years, 73% age ≥65 years

Unpublished data from: Falsey AR, et al. N Engl J Med. 2005;352(17):1749–1759.