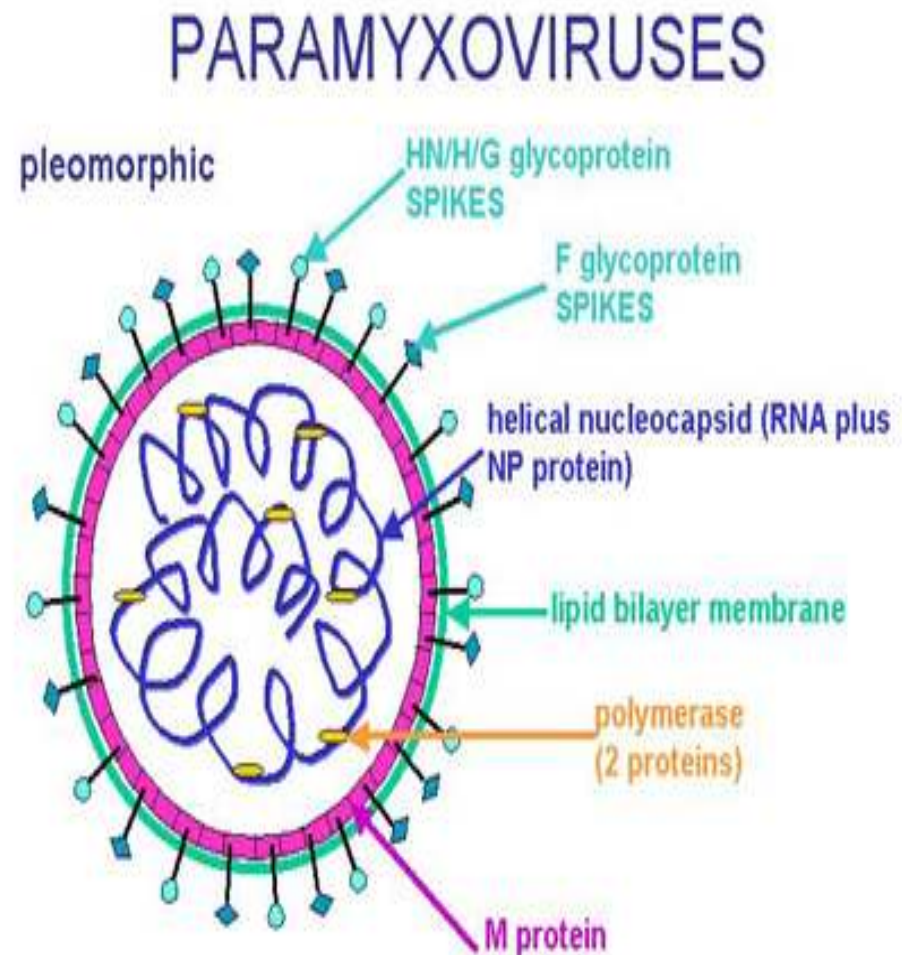


RSV λοίμωξη. Ποιός κινδυνεύει περισσότερο;

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RSV: Viral Structure and Characteristics

- There is a single antigenic type of RSV, divided into two subgroups, A and B.
- Usually one of these groups predominates on an epidemic.
- The attachment glycoprotein (G) and the fusion (F) glycoprotein are the two major glycoproteins on the surface of RSV. They control the initial phases of infection
- F protein is the main target for antiviral development.
- Both G and F glycoproteins are targeted by neutralizing antibodies during natural infection



Epidemiology-transmission

- Close contact with an infected individual or direct inoculation into the eyes and nose of infectious secretions.
- Large-particle aerosols by coughs and sneezes of an ill person may transmit RSV to others within a radius of about 3 feet.
- By touching objects that have been contaminated with infectious secretions, followed by self-inoculation into the eyes or nose.

Epidemiology

- Prevalence
 - Winter months
 - Most frequently transmitted between family members and hospitals
 - Strain A more prevalent than Strain B
- The average incubation period 2 - 8 days.
- Shedding duration is typically 7 to 10 days

Epidemiologic Manifestations

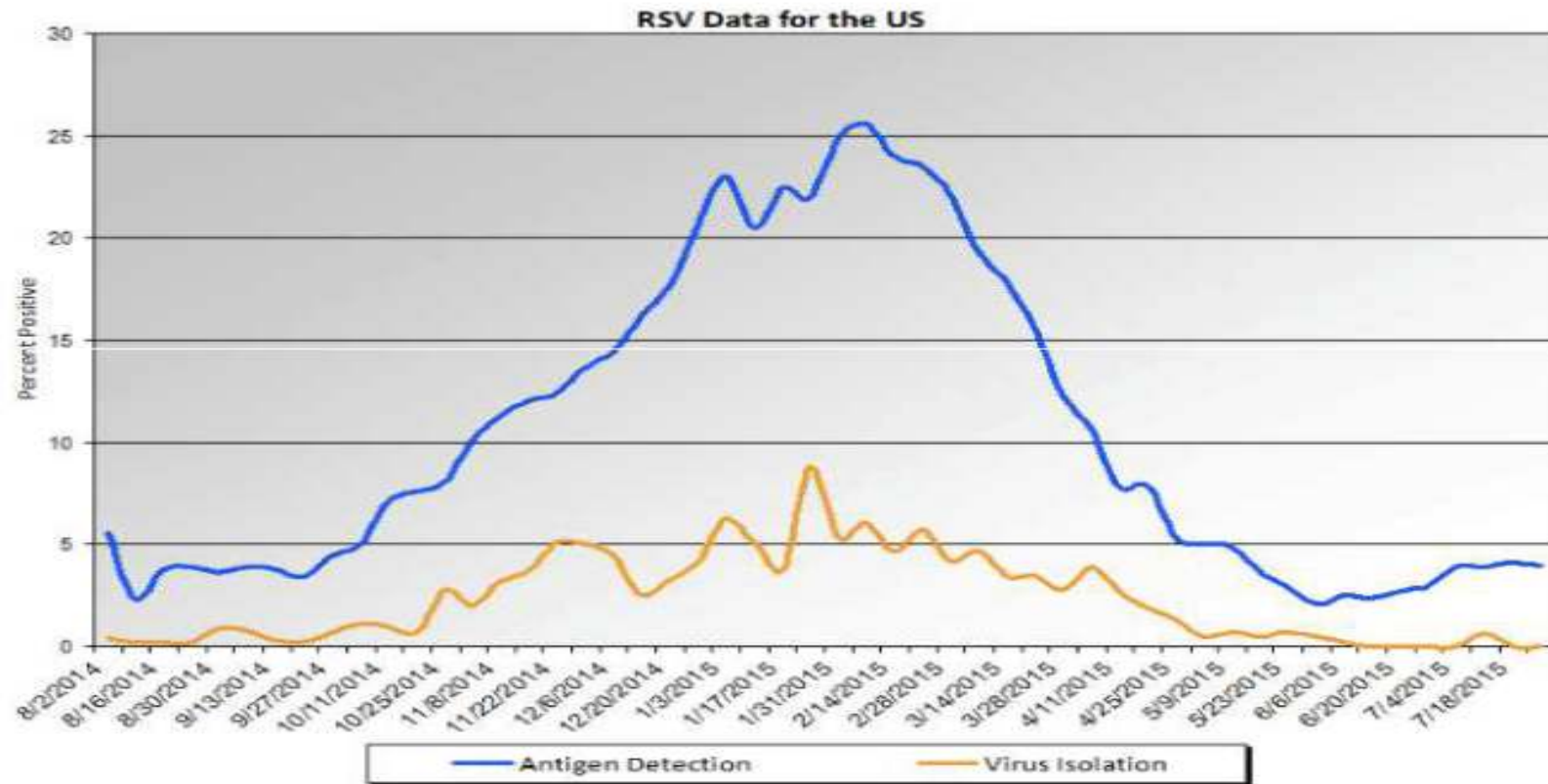
- RSV outbreaks may vary year to year in size.
- Severe LRTI from RSV occurs most frequently in the first year of life and is almost always associated with primary infection.
- All children have experienced RSV infection within the first several years of life one or more times.
- Repeated infections are common not only among young children but throughout life.

Infections among adults

- Adults also may have repetitive RSV infection
- The lack of durable immunity is illustrated by a study of 15 healthy adults who became ill with a community-acquired RSV. They were challenged with RSV of the same strain group (A) at 2, 4, 8, 14, 20, and 26 months after natural infection.
- Within 2 months of their natural infection, 47% became reinfected, and
- by 8 months, two thirds had been reinfected.

RSV Seasonality

Respiratory Syncytial Virus (RSV)



CDC Viral Disease Surveillance Network

- Infections occur year-round but peak during the cold season
- If RSV surveillance is conducted only during influenza season the burden of disease may be underestimated



Global, regional, and national disease burden estimates of acute lower respiratory infections due to respiratory syncytial virus in young children in 2015: a systematic review and modelling study

Summary

Background We have previously estimated that respiratory syncytial virus (RSV) was associated with 22% of all episodes of (severe) acute lower respiratory infection (ALRI) resulting in 55 000 to 199 000 deaths in children younger than 5 years in 2005. In the past 5 years, major research activity on RSV has yielded substantial new data from developing countries. With a considerably expanded dataset from a large international collaboration, we aimed to estimate the global incidence, hospital admission rate, and mortality from RSV-ALRI episodes in young children in 2015.

Methods We estimated the incidence and hospital admission rate of RSV-associated ALRI (RSV-ALRI) in children younger than 5 years stratified by age and World Bank income regions from a systematic review of studies published between Jan 1, 1995, and Dec 31, 2016, and unpublished data from 76 high quality population-based studies. We estimated the RSV-ALRI incidence for 132 developing countries using a risk factor-based model and 2015 population estimates. We estimated the in-hospital RSV-ALRI mortality by combining in-hospital case fatality ratios with hospital admission estimates from hospital-based (published and unpublished) studies. We also estimated overall RSV-ALRI mortality by identifying studies reporting monthly data for ALRI mortality in the community and RSV activity.

Findings We estimated that globally in 2015, 33·1 million (uncertainty range [UR] 21·6–50·3) episodes of RSV-ALRI, resulted in about 3·2 million (2·7–3·8) hospital admissions, and 59 600 (48 000–74 500) in-hospital deaths in children younger than 5 years. In children younger than 6 months, 1·4 million (UR 1·2–1·7) hospital admissions, and 27 300 (UR 20 700–36 200) in-hospital deaths were due to RSV-ALRI. We also estimated that the overall RSV-ALRI mortality could be as high as 118 200 (UR 94 600–149 400). Incidence and mortality varied substantially from year to year in any given population.

Interpretation Globally, RSV is a common cause of childhood ALRI and a major cause of hospital admissions in young children, resulting in a substantial burden on health-care services. About 45% of hospital admissions and in-hospital deaths due to RSV-ALRI occur in children younger than 6 months. An effective maternal RSV vaccine or monoclonal antibody could have a substantial effect on disease burden in this age group.

The Burden of Respiratory Syncytial Virus Infection in Young Children

- 5067 children enrolled in the study
 - 919 (18%) had RSV infections.
 - 20% of hospitalizations
 - 18% of emergency department visits
 - 15% of office visits for acute respiratory infections from November through April.
- Average annual hospitalization rates were 17 per 1000 children under 6 months of age and 3 per 1000 children under 5 years of age.
- Most of the children had no coexisting illnesses.
- Only prematurity and a young age were independent risk factors for hospitalization.

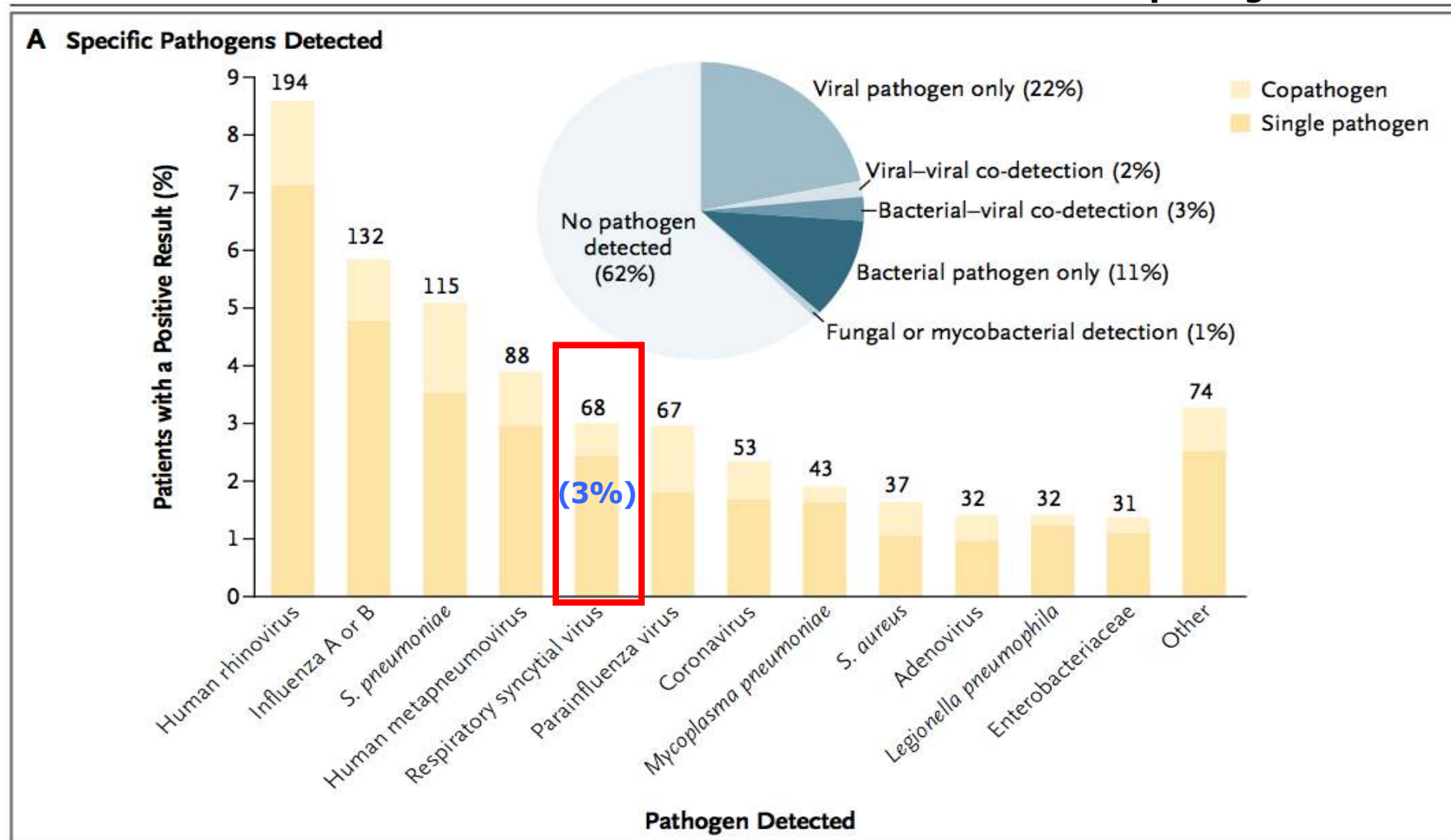
Hall et al. N Engl J Med 2009;360:588-98.

RESEARCH ARTICLE

The epidemiology of medically attended respiratory syncytial virus in older adults in the United States: A systematic review

- 10 studies - RSV was the causative agent in
- 12% of older adults with respiratory illness unselected for comorbidities
- RSV incidence among older adults increased with increasing age.
- 16% of lung transplant recipients.
- 8-13% of hospitalized adults with chronic cardiopulmonary diseases during winter seasons.
- Hospitalizations for RSV in older adults typically lasted 3 to 6 days,
- substantial proportions ICU and mechanical ventilation.
- Mortality rate was 6 - 8%.

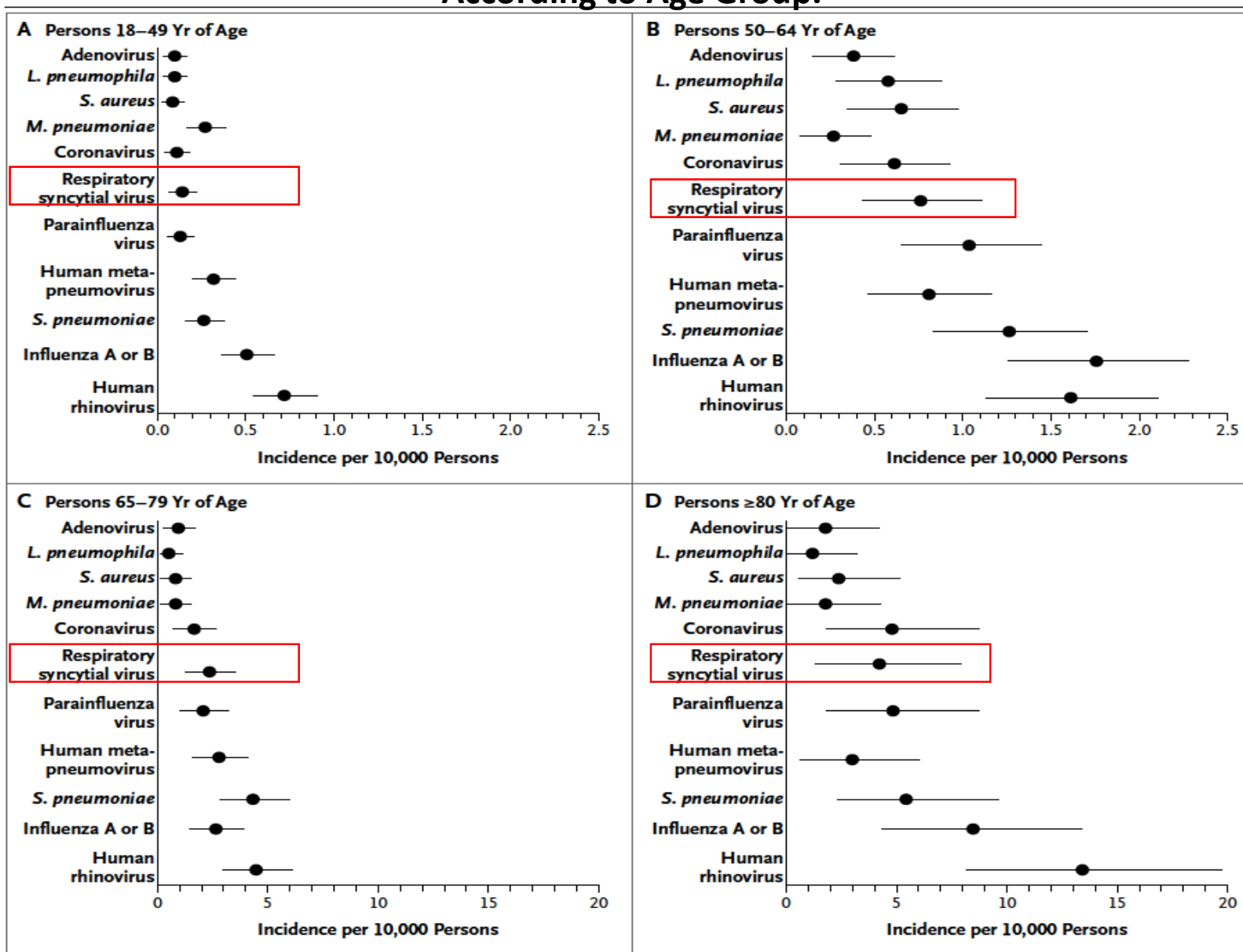
A total of 966 pathogens were detected in 853 (38%) of 2259 adults with pneumonia who had tests available for the detection of both bacterial and viral pathogens.



Rhinovirus (9%), influenza virus (6%), *S pneumoniae* (5%) and the three atypical agents (*Chlamydia pneumoniae*, *Legionella*, and *Mycoplasma pneumoniae*) accounted for only 4%

Community-Acquired Pneumonia Requiring Hospitalization among U.S. Adults

Estimated Annual Pathogen-Specific Incidence Rates of CAP Requiring Hospitalization, According to Age Group.



Case definition

- **WHO “Extended SARI” case definition for hospital-based surveillance for severe RSV infection**

- severe - defined as requiring hospitalization
- acute - defined as onset within the last 10 days
- respiratory infection - defined as having cough [in some sites cough or shortness of breath].
- **In infants less than 6 mo, additionally include those who present with**
- apnoea - defined as temporary cessation of breathing from any cause, and/or
- sepsis - defined as
 - fever (37.5 ° C or above) or hypothermia (less than 35.5 ° C), and
 - shock (lethargy, fast breathing, cold skin, prolonged capillary refill, fast weak pulse), and
 - seriously ill with no apparent cause

https://www.who.int/influenza/rsv/rsv_case_definition/en/

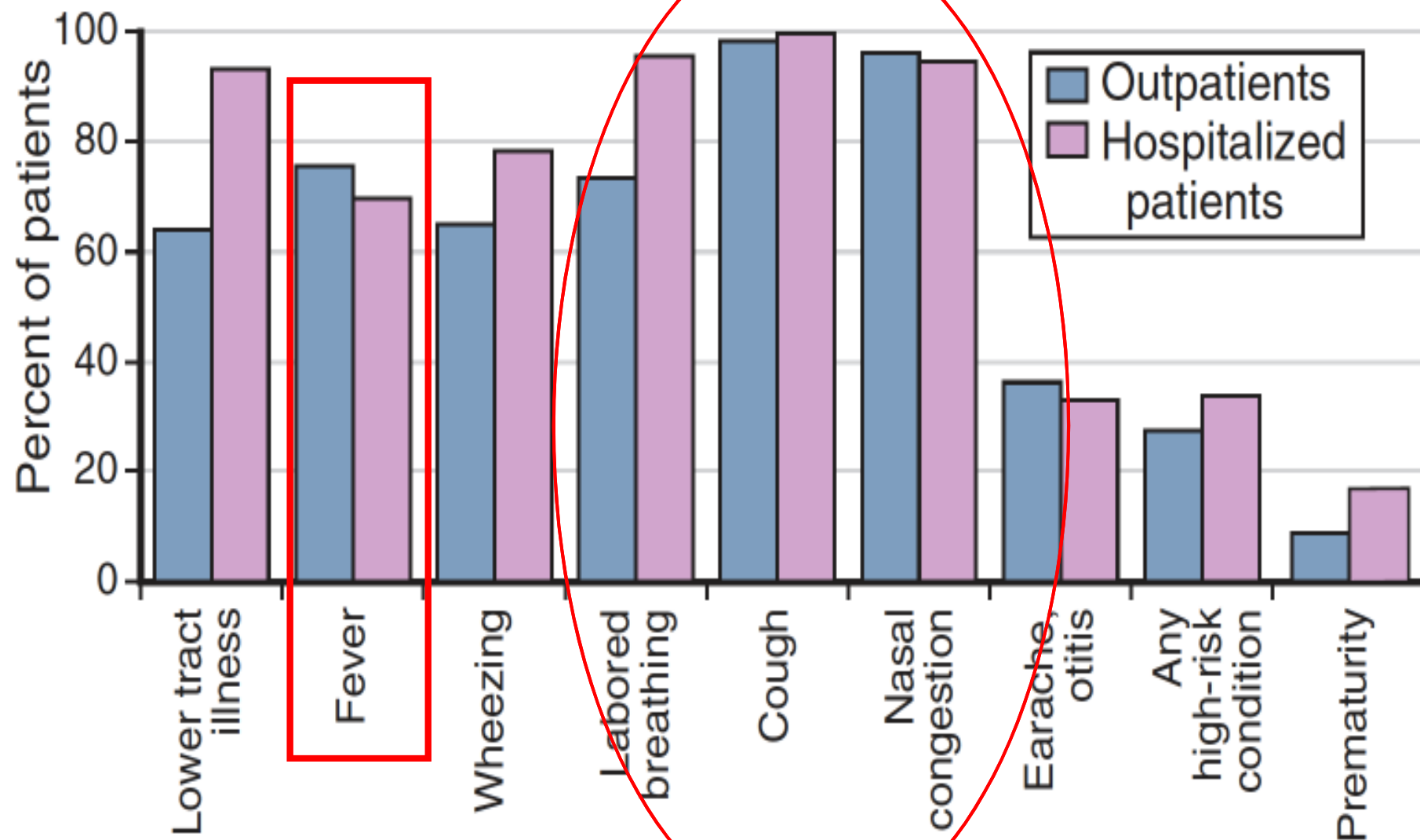
Clinical Manifestations

- Occurs within either days or hours of exposure
- Vary from person to person
- Symptoms are often severe in children <2 years old
- Symptoms are mild in adults and children

RSV infection among children

- RSV infection can cause a variety of respiratory illnesses in infants and young children.
- **In infants** primary infections with RSV frequently involve the LRTI
 - Pneumonia or bronchiolitis has been estimated to occur in 30 - 71%, depending on the age and population
- **Among young children and older individuals usually starts** with an URTI
 - Acute otitis media is a common
 - Recurrent infections URTIs
- **20 - 50%** of recurrent infections among **preschool-aged children** involve the lower respiratory tract

Clinical characteristics of children < 5 years with RSV who were outpatients, compared with those who were hospitalized



Severe disease-children

- Severe disease most commonly occurs in very young infants.
- Premature infants
- Very young infants <6 months
- Children <2 years old with chronic lung or heart disease
- Children with suppressed immune systems
- Children who have neuromuscular disorders, including those who have difficulty swallowing or clearing mucus secretions

Clinical Manifestations

Respiratory Syncytial Virus Infections in Previously Healthy Working Adults

Table 2. Type of acute respiratory infection in adults with respiratory syncytial virus (RSV) infection.

Type of acute respiratory illness	No. of patients	Percentage with symptomatic RSV infection (<i>n</i> = 177)	Percentage of all patients with RSV infection (<i>n</i> = 211)
Asymptomatic	34	—	16
Symptomatic	177	—	84
Upper respiratory tract	131	74	62
With fever	52	29	25
Without fever	79	45	37
Lower respiratory tract	46	26	22
Tracheobronchitis	36	20	17
Wheezing	10	6	5

RSV infections among adults accounted for

- 10% hospitalizations for pneumonia
- 11,4 for COPD
- 5 % for CHF
- 5 - 27% of respiratory infections in long-term care facilities.
- Risk for severe RSV infection is
 - older adults, especially those 65 years and older
 - adults with chronic lung or heart disease
 - adults with weakened immune systems

Respiratory Syncytial Virus (RSV) Compared with Influenza among Hospitalized Adults

Characteristics	RSV (N=132)	Influenza A (N=144)
Age — yr	76±13	76±12
Female sex — no. (%)	84 (64)	81 (56)
Race or ethnic group — no. (%)		
White	117 (89)	125 (87)
Black	10 (8)	12 (8)
Hispanic	5 (4)	6 (4)
Other	0	1 (1)
Chronic illness — no. (%)		
Any cardiac disease	71 (54)	71 (49)
Congestive heart failure	39 (30)	33 (23)
Any lung disease	77 (58)	79 (55)
Any heart or lung disease	106 (80)	113 (78)
Diabetes mellitus	35 (27)	28 (19)
Residence in a long-term care facility — no. (%)	16 (12)	15 (10)
Smoking (current or past) — no. (%)	88 (67)	98 (68)
Previous vaccination — no. (%)		
Influenza vaccine	99 (75)	98 (68)
Pneumococcal vaccine	94 (71)	86 (60)
Katz ADL score — mean ±SD	1.2±2.4	1.3±3.0
IADL score — mean ±SD	4.1±4.1	3.3±4.0
Length of hospital stay — days	14±41†	8±5
Bacterial infection — no. (%)		
Sputum pathogen	20 (15)	17 (12)
Blood culture positive	4 (3)	1 (<1)
Findings on chest radiography — no. (%)		
Infiltrate found	41 (31)	43 (30)
Congestive heart failure	17 (13)	15 (10)
Other	24 (18)	27 (19)
Admission to intensive care unit — no. (%)	20 (15)	17 (12)
Use of mechanical ventilation — no. (%)	17 (13)	15 (10)
Higher level of care at discharge than at admission — no. (%)	7 (5)	8 (6)
Death — no. (%)	10 (8)	10 (7)

Table 3. Influence of various factors on risk of hospitalization with respiratory syncytial virus (RSV) infection, determined by logistic-regression analysis of 124 RSV-infected subjects.

Risk factor	OR (95% CI)	<i>P</i>
Age ≥ 65 years	0.23 (0.07–0.80)	.022
Male	1.93 (0.69–5.41)	.209
Chronic pulmonary disease	2.56 (0.89–7.29)	.078
Coronary artery disease	0.87 (0.28–2.72)	.816
Congestive heart failure	1.30 (0.35–4.86)	.698
Diabetes mellitus	1.00 (0.27–3.67)	.998
Functional score per integer increase in IADL score	1.79 (1.28–2.51)	.0008
Neutralizing antibody titer $<10 \log_2$	3.59 (1.26–10.27)	.018

Immunocompromised patients

- High morbidity and mortality in patients receiving solid-organ and hematopoietic cell transplantation (HCT) with more intensive chemotherapy regimens
- The reported frequency of RSV infection varies 2 - 50%.
- Mortality rate of about 9 - 18%.
- RSV is often introduced onto wards by medical staff, visitors and spread may be rapid and difficult to control and accompanied by appreciable morbidity and mortality.

Table 2. Risk Factors of Respiratory Syncytial Virus–Associated Complications in Hematopoietic Stem Cell Transplantation Patients

Progression to LRTID

- Lymphopenia $<0.2 \times 10^9/\text{L}$
- Older age
- Mismatched/unrelated donor
- Allogeneic HSCT <1 mo
- Neutropenia $<500/\mu\text{L}$
- No therapy with aerosolized ribavirin + IVIG

Mortality

- Preengraftment
- Lymphopenia $<0.2 \times 10^9/\text{L}$
- Allogeneic HSCT <1 mo
- Severe immunodeficiency
- Older age (>65 y)

RSV in patients with HSCT and/or HM

- Occur in 1-12% of adult patients with hematologic malignancy and HSCT
- Progression to LRTID is observed in 38% (mean; range, 0%–68%) of leukemia and HSCT patients,
- Mortality of 32% (range, 0%–70%)

Table 1. Incidence rates of respiratory syncytial virus infections and lower respiratory tract infections among symptomatic hematopoietic cell transplant recipients.

Date of publication	Country	Study type	Detection methods	Percentage of allogeneic HCT	Total number of RSV cases (%)	Percentage of LRTI	Authors
1991	USA	Retrospective observational	RSV antigen and viral culture	73%	3 (5%)	33%	Garcia <i>et al.</i> ¹⁸
1996	USA	Retrospective observational	RSV antigen, viral culture and pathology	52%	33 (49%)	61%	Whimbey <i>et al.</i> ²¹
2001	Multiple European nations	Prospective observational	RSV antigen and viral culture	90%	20 (10%)	60%	Ljungman <i>et al.</i> ⁵
2002	England	Retrospective observational	RSV antigen and viral culture	100%	13 (37%)	46%	Chakrabarti <i>et al.</i> ²²
2002	USA	Retrospective observational	RSV DFA, RSV antigen and viral culture	89%	48 (9%)	52%	Small <i>et al.</i> ²²
2003	Brazil	Prospective observational	RSV antigen	72%	27 (40%)	56%	Machado <i>et al.</i> ²⁷
2003	USA	Prospective observational	Viral culture and RSV PCR	45%	11 (30%)	36%	Roghmman <i>et al.</i> ²⁹
2003	England	Retrospective observational	RSV antigen and viral culture	83%	6 (21%)	33%	Hassan <i>et al.</i> ²⁶
2005	Spain	Prospective observational	RSV antigen and viral culture	54%	19 (11%)	37%	Martino <i>et al.</i> ²⁸
2009	Sweden	Retrospective observational	RSV antigen and viral culture	100%	32 (12%)	44%	Avetisyan <i>et al.</i> ²⁴
2013	Brazil	Retrospective observational	RSV PCR	29%	14 (14%)	NA	Moreira <i>et al.</i> ⁸
2014	Italy	Prospective observational	RSV PCR	95%	21 (8%)	11%	Mikulska <i>et al.</i> ⁷

Among children with HIV infection, RSV was the most frequent identified cause of viral respiratory disease

TABLE 1. Clinical Syndromes Associated With Respiratory Viral Infections in Immunocompromised Children

Virus and Clinical Manifestations	No. (%)	No. With HIV Infection	No. With Anticancer Therapy
RSV (N = 23; 43%)			
Upper respiratory infections	10 (44%)	5	5
Bronchiolitis/Bronchitis	4 (17%)	3	1
Pneumonia	7 (30%)	3	4
Other	2 (9%)	2	
Influenza A virus (N = 14; 26%)			
Upper respiratory infections	9 (65%)	3	6
Bronchiolitis/Bronchitis	2 (14%)	1	1
Pneumonia	2 (14%)	2	
Other	1 (7%)	1	
Adenovirus (N = 7; 13%)			
Upper respiratory infections	5 (72%)	2	3
Bronchiolitis/Bronchitis	1 (14%)	1	1
Pneumonia	0		
Other	1 (14%)		
Parainfluenza 3 (N = 7; 13%)			
Upper respiratory infections	4 (58%)	2	2
Bronchiolitis/Bronchitis	0		
Pneumonia	2 (28%)	1	1
Other	1 (14%)	1	
Influenza B (N = 2; 3,7%)			
Upper respiratory infections	2 (100%)	2	

- 53 respiratory viral infections were identified:
- 26 (20%) in 129 HIV-infected children
- 27 (12%) in 218 children with cancer
- 40% of these infections are hospital-acquired that emphasizes the need for isolation and preventive measures.

RSV Infections in Children With Acute Myeloid Leukemia

TABLE 1. RSV Infections and Deaths on AAML03P1, CCG 2961, and CCG 2891

	AAML03P1	CCG 2961	CCG 2891	Total
Characteristics of all patients				
Included	De novo	De novo	De novo	De novo
No. of total patients	341	901	836	2,078
No. of patients				
<1-year of age	39	101	79	219
<2 years of age	78	193	177	448
<2.5 years of age	86	227	207	520
Median age (years)	9.5	9.5	7.6	8.7
Characteristics of patients with RSV				
No. of subjects with RSV infections	6	25	4	35
Median age (range) of those with RSV in years	6.7 years (0.76–17.99)	2.1 years (0.24–16.82)	4.9 years (0.68–16.21)	2.2 years (0.24–17.99)
No. with RSV by age				
<1-year of age	1	5	1	7
<2 years of age	1	12	2	15
<2.5 years of age	1	16	2	19
No. of subjects with RSV infections November 1–March 31	6	19	4	29
No. died of RSV ^a	1	3	0	4
Percentage of all treated patients who died of RSV	0.3%	0.3%	0%	0.2%

The prevalence of RSV infection ranged from 0% to 1% in induction and between 0.3 and 2.2% in consolidation. RSV infections and deaths are rare in pediatric AML

Sung et al. *Pediatr Blood Cancer* 2008;51:784–786

Respiratory Viral Infections in Adults With Hematologic Malignancies and Human Stem Cell Transplantation Recipients

TABLE 1. Distribution of Respiratory Viral Infections (343 patients)

	Influenza A No. (%)	Influenza B No. (%)	Parainfluenza No. (%)	RSV No. (%)	Picornavirus No. (%)	Total (%)
No. of cases	72 (21)	40 (12)	92 (27)	107 (31)	32 (9)	343
URI only	47 (21)	31 (14)	58 (26)	68 (30)	20 (9)	224 (65)
Pneumonia	25 (21)	9 (8)	34 (29)	39 (33)	12 (10)	119 (35)
Deaths*	3 (19)	2 (12)	4 (25)	7 (44)	0 (0)	16 (5)
Age ≥65 yr	12 (31)	4 (10)	9 (23)	12 (31)	2 (5)	39 (11)
Age <65 yr	60 (20)	36 (12)	83 (27)	95 (31)	30 (10)	304 (89)
Male/female	38/34	26/14	57/35	60/47	23/9	204/139 (59/41)
HSCT	43 (19)	24 (10)	65 (28)	75 (33)	23 (10)	230 (67)
Leukemia	10 (16)	10 (16)	17 (28)	18 (30)	6 (10)	61 (18)
Lymphoma	9 (33)	3 (11)	6 (22)	6 (22)	3 (11)	27 (8)
Hodgkin disease	4 (40)	3 (30)	1 (10)	2 (20)	0 (0)	10 (3)
Myeloma	6 (40)	0 (0)	3 (20)	6 (40)	0 (0)	15 (4)

Lack of RSV-directed antiviral therapy ($p = 0.025$) and age ($p = 0.042$) were associated with development of RSV pneumonia

Lymphocytopenia was a significant risk factor for LRTI in patients with RSV infections

Table 3 Risk factors for lower respiratory tract infection

	<i>OR (95% CI)</i>	<i>P value</i>
<i>All episodes</i>		
Lymphocytopenia	2.52 (1.26–5.06)	0.008
Neutropenia	0.82 (0.68–0.99)	0.04
Donor	0.99 (0.57–1.72)	0.99
<i>RSV</i>		
Lymphocytopenia	3.04 (1.26–7.35)	0.01
Neutropenia	0.82 (0.66–1.01)	0.06
Donor	0.75 (0.35–1.59)	0.45
<i>Influenza A or B</i>		
Lymphocytopenia	2.84 (0.73–11.01)	0.11
Neutropenia	0.87 (0.66–1.15)	0.06
Donor	0.99 (0.42–2.40)	0.45

Burden of severe RSV disease among immunocompromised children and adults: a 10 year retrospective study

- From 239 RSV-positive immunocompromised patients 175 were adults and 64 children of whom 111 (47.8%) presented with LRTI.
- **Immunocompromised children** were more likely to be admitted to hospital compared to adults (75% vs 62.9%, $p = 0.090$) but...
- **Adults** patients were more frequently admitted to the ICU (17/19) OR died (11/11).

Table 2 Clinical outcomes of immunocompromised patients with RSV infection

Variable, Number; (%) unless indicated otherwise	Children (N = 64)	Adult (N = 175)	p value	Total (N = 239)
All-cause admission to hospital (adults: 5 missing values)	48 (75.0)	107 (62.9)	0.090	155 (66.2)
ARTI-attributable hospital admission ^a (adults: 5 missing values)	31 (48.4)	58 (34.1)	0.050	89 (38.0)
• Length of hospital stay (d) mean (SD) ^a	• 5 (3.5)	• 9 (12.0)	• < 0.001	• 7 (9.0)
• Admission to the ICU ^a	• 2 (6.5)	• 17 (29.3)	• 0.014	• 19 (21.3)
• Use of mechanical ventilation ^a	• 1 (3.2)	• 13 (22.4)	• 0.029	• 14 (15.7)
• Mortality within 30 days of admission ^a	• 0	• 11 (19.0)	• 0.007	• 11 (12.4)
All-cause mortality within 30 days of admission	1 (1.6)	20 (11.4)	0.018	21 (8.8)
LRTI ^b (adults: 7 missing values)	26 (40.6)	85 (50.6)	0.188	111 (47.8)
RSV-attributable pneumonia ^b	12 (18.8)	62 (36.9)	0.008	74 (31.9)
• RSV documented from BAL ^b	2 (16.7)	23 (37.1)	0.024	25 (33.8)
• RSV-bacterial co-infection documented from BAL	0	7 (11.3)	0.020	7 (9.5)

Diagnosis

- RSV infection among young children is most often diagnosed clinically in the setting of the community's RSV season.
- Among adults, however, the findings are less specific, and RSV is commonly not suspected.
- Laboratory diagnosis may be made by
 - viral isolation
 - rapid diagnostic tests
 - Perform poorly in adults, elderly and immunocompromised because of the low viral titers in secretions
 - RT-PCR, or
 - serology

Treatment

- No treatment given in mild disease
- Ribavirin aerosol
 - for children who have severe disease
- immune globulin
 - The results with either polyclonal IVIG or the anti-F monoclonal antibody (palivizumab) alone or in combination with ribavirin have been mixed, with some studies suggesting a trend toward diminished morbidity and progression to LRTI when used therapeutically



Respiratory Syncytial Virus



Primary Regimens

- Treatment:
 - Hydration, supplemental oxygen.
 - Routine use of Ribavirin is not recommended outside of HSCT and lung transplant
 - Retrospective multivariate analysis of aerosolized Ribavirin in HSCT patients indicates improved survival and reduced mortality, $p < 0.0001$: Clin Infect Dis 57:1731, 2013. Benefit appears greater in preventing progression of upper tract disease to lower tract than in improving outcome in LRTI (reviewed in BMJ. 2019 Sep 10;366:l5021)
- Prevention:
 - Palivizumab (Synagis) 15 mg/kg IM once per month November-April for specific infants who qualify for 5 doses (Pediatrics 124:1694, 2009)
 - Timing of coverage may need to be adjusted in some regions based on reported cases in the region, as opposed to using fixed dosing schedules (Pediatrics 126:e116, 2010).

Alternative Regimens

- None

[Top](#)

Antimicrobial Stewardship

Prophylaxis

- Palivizumab does not prevent infection but is associated with
 - diminished clinical severity,
 - Diminished the risk for developing LRTI
 - Diminished need for hospitalization.

Prevention

- **No RSV vaccine available**
- Frequent hand washing
- At-Risk children injection of RSV antibodies monthly during peak season.
- Keeping school-age children away from younger siblings (anyone under 2 years of age) if cold symptoms are present
- Minimize number of visitors with the infant
- Avoid crowded places
- If possible, don't take child to daycare during RSV season

Conclusions

- Respiratory syncytial virus (RSV) causes acute upper and lower tract respiratory illnesses
- It is one of the leading causes of death of infants <1 year of age worldwide
- Adults with comorbidities, elderly and immunocompromised patients are at increased risk severe RSV infection