RSV: Burden of Disease in Older Adults

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Disclosures

• I provide consulting services for most vaccine manufacturers, including those that market RSV vaccines (GSK, Pfizer)

• I will not discuss vaccines in this presentation
Objectives

• Provide context for the burden of RSV disease in older adults with Influenza and SARS-CoV-2 infection
Seasonal Flu, RSV

Deadlier

More Contagious

Mortality (%)

Average number of people infected by each sick person

References:
1. Adapted from the New York Times' graphic compiled from CDC and US and international health agencies with RSV information, and:
Fun Fact

- Infants have nearly all of the airways and alveoli they will have as adults
  - This means a huge surface area to volume and especially tiny airways
- This means that it takes less inflammation and bronchospasm to cause obstruction that results in wheezing and croup
- It’s one of three reasons children present differently from older adults with RSV infection

Reference:
Risk Factors for Severe RSV Infection

- Age
- Overcrowding
- Smoke exposure (cooking, tobacco)
- Low socioeconomic status
- Asthmatic mother (for risk in children)
- *Co-morbidities* (and in older adults, *multimorbidity*)
Susceptibility in Older Adults

- RSV is among the top four causes of ILI (third before the advent of SARS-CoV-2), after enterovirus and influenza
  - But RSV was the second most common cause of hospitalization
    - Twice as likely as patients who had laboratory confirmation of influenza
- 95% of children have had RSV by age 2
  - Essentially all adults have survived prior RSV, and will have some underlying immunity
- P&I start increasing around age 50
  - Immune senescence
    - In elderly, greater susceptibility with lower RSV-specific Ig and nasal IgA
    - T-cell immunity declines with age

ILI, influenza-like illness

References:
Susceptibility

- RSV is among the top four causes of ILI (third before the advent of SARS-CoV-2), after enterovirus and influenza.
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- 95% of children have had RSV by age 2.
  - Essentially all adults have survived prior RSV, and will have some underlying immunity.
- P&I start increasing around age 50.
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    - In elderly, greater susceptibility with lower RSV-specific Ig and nasal IgA.
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ILI, influenza-like illness

References:
# Biologic Changes With Age Relate to Clinical Presentation

<table>
<thead>
<tr>
<th>Biologic Change</th>
<th>Clinical effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduced IL-6</td>
<td>Reduced fever, less efficient viral clearance</td>
</tr>
<tr>
<td>Impaired respiratory tract mucociliary function</td>
<td>Reduced cough, less efficient viral and mucous clearance</td>
</tr>
<tr>
<td>Delayed cytokine increase</td>
<td>Fewer symptoms at onset</td>
</tr>
<tr>
<td>Delayed cytokine normalization</td>
<td>Slower improvement and prolonged pro-inflammatory state</td>
</tr>
<tr>
<td>Reduced T-cell help</td>
<td>Reduced response to infection, vaccination; less durable</td>
</tr>
<tr>
<td>Brain Aging</td>
<td>Risk for delirium, sleep/appetite disturbance with cytokine storm</td>
</tr>
</tbody>
</table>

Reference:
Fun Fact

- Immune senescence is the second of three reasons why children present differently from older adults
  - Children produce more cytokine faster (therefore faster and higher fever), and other cytokine-mediated symptoms
  - Children may not have prior immunity, increasing peak viral shedding titers
Many Clinicians Don’t Recognize that RSV is a Big Deal for Older Adults

- Each year, up to 10% of older adults are infected with RSV in the US
  - Closer to 10% in settings with close quarters (e.g., nursing homes, assisted living and senior housing)
- Older adults more likely than younger adults to be hospitalized or die

<table>
<thead>
<tr>
<th>Associated Risk Condition</th>
<th>Odds Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke, heart failure, chronic lung disease</td>
<td>~2 (1.02-4)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Solid organ transplant</td>
<td>2.52 (0.88-7.22)</td>
<td>0.085</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>4.37 (2.74-6.98)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hematologic malignancy</td>
<td>5.17 (2.02-13.20)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

References:
Chronic Conditions as Risk Factors for RSV-Associated Hospitalization

- CDC/ACIP Evaluated 9 conditions as risk factors for RSV hospitalization
  - Asthma
  - Chronic kidney disease (CKD)
  - Chronic obstructive pulmonary disease (COPD)
  - Coronary artery disease (CAD)
  - Current smoking
  - Diabetes mellitus
  - Obesity (body mass index 30-39 kg/m²)
  - Severe obesity (body mass index ≥40 kg/m²)
  - Stroke

Reference:
Chronic Conditions as Risk Factors for RSV-Associated Hospitalization

- Compared RSV-associated hospitalization in older adults between people with and without those conditions
  - Numerator
    - RSV-NET for RSV hospitalizations
      - >300 hospitals, about 8.6% of US population
      - RSV + test in two weeks prior to hospitalization
  - Denominator
    - Behavioral Risk Factor Surveillance System (BRFSS)
    - Census population counts
    - Annual telephone surveillance with self reported conditions representative of state populations

Reference:
RSV-linked hospitalization in community elderly 2017-2018 vs without condition: adjusted rate ratio

*Preliminary Data

<table>
<thead>
<tr>
<th>Age</th>
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<tbody>
<tr>
<td>50-64 aRR</td>
<td>~75</td>
<td>7.9</td>
<td>4.2</td>
<td>5.8</td>
<td>3.3</td>
<td>2.4</td>
<td>3.7</td>
<td>2.8</td>
<td>1.4</td>
</tr>
<tr>
<td>Per 100k</td>
<td>~340</td>
<td>~290</td>
<td>~80</td>
<td>~210</td>
<td>~140</td>
<td>~250</td>
<td>~250</td>
<td>~200</td>
<td>~180</td>
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- Rate/100k for hospitalization increases between ages 50-64 to 65-74, and for 65-74 to >75 for conditions of CKD, severe obesity, COPD, asthma

- Shaded values confidence intervals cross 1

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<td>65-74 aRR Per 100k</td>
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<td>6.1</td>
<td>4.5</td>
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<td>3.3</td>
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<td>2.5</td>
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<tr>
<td></td>
<td>~550</td>
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<td>2.5</td>
<td>2.2</td>
<td>1.6</td>
</tr>
<tr>
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<td>~550</td>
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<td>~150</td>
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<td>2.9</td>
<td>1.1</td>
<td>4.2</td>
<td>0.9</td>
<td>1.9</td>
<td>1.6</td>
<td>1.9</td>
</tr>
<tr>
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<td>~1300</td>
<td>~900</td>
<td>~300</td>
<td>~900</td>
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<td>~500</td>
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- 95% of children have had RSV by age 2
- P&I begin increasing around age 50
  - Immune senescence
    - In elderly, greater susceptibility with lower RSV-specific Ig and nasal IgA
    - T-cell immunity declines with age: reduced CD8 cytotoxic T-cell function; shift Th1 to Th2
  - Decline in DC function
- Older adults with severe RSV do show CD4 and CD8 T-cell responses but unclear if severe disease is due to immunosenescence or “just” impaired T-cell responses and/or dysfunctional antibody

References:
Clinical Considerations

● Include RSV in differential diagnosis if it’s “in season”
  ○ RSV season starts with influenza and beta-coronavirus season, but may last 1-2 months longer (Nov-May)
    ■ Adenovirus and human metapneumovirus circulates all year
    ■ Rhinovirus and parainfluenza circulate mostly late spring to fall
  ○ More likely to be RSV if known RSV-infected contact
  ○ For adults, prior RSV infection does not reduce likelihood of future RSV infection

● In healthy adults, usually mild URI with symptoms clearing in about 5 days
  ○ Wheezing, cough less common

● In adults with underlying heart or lung disease, weakened immune system, may present with lower respiratory tract infection
  ○ Asthma, COPD, HF
  ○ Wheezing, cough common

● Viral shedding longer in older adults and infants
COVID, Flu & AMI

- COVID associated with strokes and heart attacks due to coagulopathy, viral invasion
- Kaiser Permanente Northern California with 4.4 million lives.¹
  - January through April 2020 (red), weekly AMI (STEMI and NSTEMI) hospitalization compared to 2019 (yellow)
  - AND COVID-19 incidence rates (blue)
  - 48% decrease in AMI hospitalization during COVID-19, both STEMI and NSTEMI
- Laboratory-confirmed influenza hospitalization (green) declined by over 90% in March
  - Opposite the increase in COVID-19 hospitalization

Figure adapted from CDC’s FluView and Solomon et al.⁴,⁵

References:
Like with influenza, RSV and other respiratory virus activity and associated hospitalizations declines with the “lockdown” response to the SARS-CoV-2 pandemic.

Reference:
Weekly hospitalization rates reported per 100,000 population in the US. Based on findings from participating sites in 58 counties in 12 states. Preliminary data are shaded in gray.

Reference:
# Estimated Impact of RSV in adults ≥ age 60 in Japan

<table>
<thead>
<tr>
<th>Parameter</th>
<th>3 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total population</td>
<td>43,681,000</td>
</tr>
<tr>
<td>RSV-ARI</td>
<td>5,311,823</td>
</tr>
<tr>
<td>RSV-URTD</td>
<td>2,783,250</td>
</tr>
<tr>
<td>RSV-LRTD</td>
<td>2,528,573</td>
</tr>
<tr>
<td>RSV-URTD-related OP visits</td>
<td>1,327,194</td>
</tr>
<tr>
<td>RSV-URTD-related hospitalizations</td>
<td>3,120</td>
</tr>
<tr>
<td>RSV-LRTD-related OP visits</td>
<td>2,130,180</td>
</tr>
<tr>
<td>RSV-LRTD-related hospitalizations</td>
<td>531,045</td>
</tr>
<tr>
<td>RSV-LRTD deaths</td>
<td>25,455</td>
</tr>
</tbody>
</table>

Reference:
RSV in Older Adults

- **RSV and influenza similar** for ICU use and mortality:\(^1\)
  - LOS longer (14 vs 8 days)
  - ICU use (15 vs 12%) and mortality (8 vs 7% similar)
- **RSV accounted for 11% of COPD exacerbations and pneumonia admissions**:\(^1\)
  - 7% of asthma and 5% of HF admissions
- Also roughly similar proportionately to influenza in proportion of hospitalized patients who have pneumonia diagnosis and getting ventilator support:\(^1\)
- **Study 842 respiratory hospitalizations (771 patients), 41% had viral infection**:\(^2\)
  - 212 hospitalizations (61% of the 348 with viral infection) had *only* a viral infection
  - **Procalcitonin** evidenced *mixed* viral/bacterial RI in 21%; these were older and often with PNA
  - 90% received *antibiotics* (both groups)
    - 4 of 10 deaths were complications of *C. difficile* colitis

References:
RSV and Acute MI

Of 277k respiratory virus tests, 19k influenza

499 of these hospitalized for AMI

Of these, 332 unique patients had flu in week before AMI

Risk AMI (incidence ratio) 6-fold higher in week after flu

Risk also increased for AMI following RSV and other viruses by about 3-fold

Reference:
“Thrombometer” – The Propensity to Clot

Increases with age
- Inflammatory markers of age
  - IL-6, IL-8, C-reactive protein

Increases with disease
- Obesity
- Diabetes
- Arthritis, vascular disease
- Dementia
- COPD

Increases following infection
- Influenza, RSV
- SARS-CoV-2
- Community acquired pneumonia
- Shingles
- Bladder infection
- Pressure sores
Influenza virus, RSV, SARS-CoV-2, etc

INFECTION

- Protein C and S
- Serum Amyloid A
- Cytokines
- Catecholamines
- Hypoxia
- Vasoconstriction
- Platelet aggregations and coronary plaque disruption
- Thrombogenesis
- Emboli

Reference (adapted from):
Fun Fact

- **Children have a better mucociliary escalator than older adults**
  - With age, fewer cells and less efficient viral clearance on top of greater likelihood of polypharmacy--including drugs that dry secretions) change ability to clear virus
  - So early, wheezing, whooping more prominent with greater consequences from inflammation and earlier coughing
  - In older adults, productive coughing likely delayed a bit in course of illness and less wheezing

- **Children also don’t typically have the other underlying conditions**
  - So diagnostic confusion for other etiology (HF or COPD exacerbation) not as easily confounded by a diagnostic heuristic
RSV in Old-Older Adults

- In the long-term care setting (a “canary in the coal mine”), RSV is particularly burdensome
- For the 6 seasons 2011-2017 of permanent nursing home residents, attributable cardiorespiratory hospitalization burden from RSV and influenza was similar

Reference:
RSV and Influenza Associated Hospitalizations Annually

<table>
<thead>
<tr>
<th>Disease Associated Hospitalizations per 1 million per year in the US</th>
</tr>
</thead>
<tbody>
<tr>
<td>RSV</td>
</tr>
<tr>
<td>1700-2800 among adults 65 years old and older</td>
</tr>
<tr>
<td>Influenza</td>
</tr>
<tr>
<td>3200-9200 among adults 65 years old and older</td>
</tr>
</tbody>
</table>

References:
Summary

- RSV relatively unrecognized as a significant burden for older adults
  - If not tested for, it won’t be recognized
- RSV a greater burden for those with underlying conditions
- Consequences of RSV infection (like for influenza) risk being under appreciated
  - For example, hospitalization following infection, heart attacks, etc.