Respiratory Disease in Older Adults

A Focus on Respiratory Syncytial Virus
Quick Audience Poll
Webinar Agenda

• The Epidemiology of Respiratory Disease and the Older Adult
• Immunology and Aging: Why Older Adults Get Respiratory Disease
• Preventing and Managing Respiratory Syncytial Virus Infections
Objectives

• State the incidence and etiologies of seasonal respiratory infections that occur commonly in adults older than 65 years of age.
• Describe patterns of infection of the respiratory syncytial virus (RSV) and related morbidity and mortality in older adults.
• List risk factors associated with more severe illness with RSV.
• Describe the pathogenesis of disease associated with respiratory infections caused by RSV.
• List therapeutic options for preventing and managing RSV infections, including those currently available in the United States and those in development.
• Formulate a clinical plan for patients with suspected RSV infections.
The Epidemiology of Respiratory Disease and the Older Adult

R. Gordon Douglas, Jr., MD
## DISCLOSURE(S)

<table>
<thead>
<tr>
<th><strong>Board of Directors:</strong></th>
<th>Protein Sciences (manufacturer of influenza vaccine)</th>
</tr>
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<tbody>
<tr>
<td><strong>Consultant:</strong></td>
<td>None</td>
</tr>
<tr>
<td><strong>Discussion of Off-Label, Investigational, or Experimental Drug Use:</strong></td>
<td>Not applicable</td>
</tr>
</tbody>
</table>
Defining Respiratory Illness

• Respiratory illnesses in older adults
• Clinical syndromes
  ➢ Upper tract—Usually mild, viral
  ➢ Lower—More serious, can be viral (influenza, RSV) but is often bacterial, or a secondary bacterial infection emerges later in disease course
  ➢ Lower can be tracheobronchitis, bronchitis, or pneumonia (hospital- or community-acquired)

Etiologies of Community-Acquired Pneumonia

Outpatients
- Streptococcus pneumoniae
- Mycoplasma pneumoniae
- Haemophilus influenzae
- Chlamydia pneumoniae
- Influenza A and B
- RSV
- Parainfluenza
- Rhinovirus

Inpatients/general wards
- Outpatient pathogens plus:
  - Legionella species
  - Aspiration

Inpatients/critical care
- Outpatient and inpatient/general pathogens plus:
  - Staphylococcus aureus
  - Gram-negative bacilli

Severity

RSV Is an Important Pathogen in the Older Adult

- Common pathogen in the winter season
- Well recognized in pediatrics but confused for other viruses in older adults
- The risk of serious illness rises with age
- Hospitalizations and deaths occur frequently
- Symptoms are very similar to those of influenza and other common respiratory pathogens
- Testing outside the research setting is expensive and rarely done
RSV Attack Rates in Older Adults

• Impact of RSV similar to nonpandemic influenza in older adults living in the community and long-term care facilities
• RSV attack rates in nursing homes are 5% to 10% per year with significant rates of pneumonia (10%–20%) and death (2%–5%)
• Highest risk of severe RSV disease in those with underlying medical conditions (COPD, incremental functional impairment, low neutralizing antibody titers)
• Surveillance data vary considerably based on methods used for diagnosis: culture, serology, RT-PCR, RSV RNA


No. All-Cause Deaths per Season


Includes deaths attributed to respiratory viral infection directly or related to underlying respiratory, circulatory, and other conditions.

Average Annual All-Cause Deaths by Age Group

Mortality rates per 100,000 person–years:

<table>
<thead>
<tr>
<th>Age</th>
<th>Influenza</th>
<th>RSV</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1</td>
<td>2.2</td>
<td>5.4</td>
</tr>
<tr>
<td>1–4</td>
<td>1.1</td>
<td>0.9</td>
</tr>
<tr>
<td>5–49</td>
<td>1.5</td>
<td>2.6</td>
</tr>
<tr>
<td>50–64</td>
<td>12.5</td>
<td>7.8</td>
</tr>
<tr>
<td>≥65</td>
<td>132.5</td>
<td>29.6</td>
</tr>
</tbody>
</table>


Includes deaths attributed to respiratory viral infection directly or related to underlying respiratory, circulatory, and other conditions.
RSV Signs and Symptoms in Older Adults

- Clinical picture indistinguishable from those of other respiratory pathogens
- Fever not as pronounced as with influenza; temperature >38°C in less than half of patients
- Nearly all patients have cough (≥90%), dyspnea reported by 11%–20% of patients, very few have gastrointestinal symptoms
- More wheezing than with influenza

Polling Question

• How do you clinically distinguish RSV from influenza?
  – RSV has more coughing
  – Flu has more wheezing
  – Determine if it's in the upper or lower tract
  – You can't clinically distinguish RSV and influenza
Immunology and Aging: Why Older Adults Get Respiratory Disease

Stefan Gravenstein, MD, MPH
Director, Center for Geriatric Medicine
University Hospitals Cleveland Medical Center
Professor of Medicine and Family Medicine
Case Western Reserve University School of Medicine
## DISCLOSURES

<table>
<thead>
<tr>
<th>Research Support:</th>
<th>Sanofi, Seqirus, CDC, NIH, MacGregor Foundation, Cleveland Foundation</th>
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<tr>
<td>Consultant:</td>
<td>Brown University, Catapult consultants, Healthcentric Advisors, Janssen, Longevoron, Pfizer, Sanofi, Seqirus</td>
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<tr>
<td>Discussion of Off-Label, Investigational, or Experimental Drug Use:</td>
<td>None</td>
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</table>
Infection Causes More Pathology With Age

- Infections
  - Influenza: A prototype
  - Shingles
  - Chickenpox
  - Hepatitis
  - *Strep. pneumoniae*

- Toxin-producing infections
  - *Clostridium difficile*
  - Tetanus
  - Diphtheria

Vaccine Is Less Effective With Age

- Vaccines vs. pathogens
  - Influenza
  - Shingles
  - Hepatitis
  - Pneumococcal

- Vaccines vs. toxins
  - *C. difficile* vaccine (in trials)
  - Tetanus
  - Diphtheria
Objectives

Understand why older adults suffer more serious outcomes with respiratory disease

• Describe the impact of vaccines, disease prevention, and benefits of immunization programs in older adults
• Understand the influence of age in immune response
• Connect aging to clinical outcomes, such as with RSV and influenza
• Connect immune response to other vaccines
Polling Question

TRUE OR FALSE ABOUT RSV?

1. More serious outcomes from infectious diseases occur primarily due to advancing age?
2. Less symptomatic in oldest and youngest
3. Increases seasonal hospitalization and mortality
<table>
<thead>
<tr>
<th>Vaccine-Preventable Diseases in the U.S. in Adults Age 65 or Older, 2013</th>
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<tbody>
<tr>
<td><strong>INCIDENCE</strong></td>
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<tr>
<td># cases</td>
</tr>
<tr>
<td>Influenza ≥65</td>
</tr>
<tr>
<td>Pneumococcal ≥65</td>
</tr>
<tr>
<td>Zoster ≥65</td>
</tr>
<tr>
<td>Pertussis ≥65</td>
</tr>
</tbody>
</table>

Influenza and Pneumonia: Influenza-Associated Mortality and Hospitalization Rates by Age

Monthly RSV Testing at UHCMC, 2014–17

The graph shows the number of RSV cases (purple bars) and the total number of tests (black line) from October 2014 to March 2017. The highest number of RSV cases occurred in December 2014 with 654 cases, while the lowest was in February 2015 with 6 cases. The total number of tests peaked in December 2016 with 506 tests, and the lowest was in February 2015 with 15 tests.
Why the Impact of Respiratory Viruses?

Host factors
- Age, health, and exposure

Environmental factors
- Exposure, humidity

Viral factors
- Antigenic variation
Host Factor: Age

- In infants and children, if no prior exposure or vaccine, no immunity
- Declining immunity (more later) with age
  - Altered presentation of disease (later diagnosis)
  - Reduced immune response to vaccines
- Difficulty in clearing virus with advanced age
  - Mucociliary escalator less efficient
  - Cough less forceful
  - Less fever, less impairment of viral replication
- Increase in underlying inflammatory markers
  - Increasingly in a “prothrombotic state”
- Change in the way people complain, accept illness
- Physiologic reserve
Host Factor: Health

- **Lung disease**
  - Affects viral clearance, pulmonary reserve, inflammatory state

- **Endocrine disease**
  - Affects immune defense mechanisms, physiologic reserve, inflammatory state

- **Obesity**
  - Affects pulmonary function, underlying inflammation

- **Pregnancy**
  - Affects pulmonary function, immune function
Environmental Factors

- **Children (why they spread disease)**
  - More virus per drop
  - Hanging out with kids, and spreading virus longer
  - Aerosolization
  - Hygiene

- **Adults (why they spread disease, too)**
  - Spreading virus better (vigor of cough, sneeze: aerosol)
  - Close contact as caregivers

- **Herd immunity: 80% of herd immune?**
  - May not apply to RSV
Funniest Flu Shot Commercial Ever!

https://www.youtube.com/watch?v=AAsK-m_HpQo
Influenza as an Example: Airborne Influenza Distribution

- Airborne particles collected in urgent care clinic using stationary and personal aerosol samplers
  - Employee and patient testing
  - 11 days, 4–5 hours per day

- Influenza A+ or B+
  - 17% of stationary samplers positive, 19% of personal samplers
  - Correlated with the location of patients with influenza \( r = 0.77 \)
  - Of samples with influenza A RNA, 42% were particles with aerodynamic diameters <4.1 µm

Numbers of Clinically Confirmed Patients With Influenza and Percentage of Influenza-Positive Aerosol Samplers, by Day

Influenza A RNA Concentrations in Various Locations of Urgent Care Clinic, by Day

Viral Factors

• Drift
  – Minor antigenic variation
  – Strains at the beginning of influenza season tend to differ from those at the end of the influenza season in minor ways

• Shift (occurs with influenza—major antigenic variation)
...in a little while you will witness something very special.
You will witness...
An amazing illusion...
An amazing change...
I will tell you what you have been thinking!
In front of you are 6 different cards.

Think of one.
Just concentrate on the one...
I will find the card in your thoughts.

Think now . . .
Think of your card the whole time......
Look!
I took your card!!!

[Playing cards image]
Antigenic Shift
## Immunology and Older Age

<table>
<thead>
<tr>
<th>Biologic Change With Age</th>
<th>Clinical Consequence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduced interleukin (IL)-2</td>
<td>Reduced T-cell help and symptoms</td>
</tr>
<tr>
<td>Reduced T-cell help</td>
<td>Reduced vaccine response (both antibody avidity and quantity)</td>
</tr>
<tr>
<td>Reduced IL-6, interferon-alpha response</td>
<td>Reduced fever</td>
</tr>
<tr>
<td>Reduced tumor necrosis factor–alpha</td>
<td>Reduced malaise and anorexia</td>
</tr>
<tr>
<td>Delayed increase and decline in inflammatory cytokines</td>
<td>Delayed symptom onset and resolution; prolonged prothrombotic state</td>
</tr>
<tr>
<td>Prothrombotic state</td>
<td>Increased risk from thrombotic outcomes (e.g., myocardial infarction, cerebrovascular accident)</td>
</tr>
<tr>
<td>Increased IL-6 and -8 baseline</td>
<td>Increased delirium from cytokines</td>
</tr>
</tbody>
</table>
## Presentation of Clinical Influenza Differs by Age Group

<table>
<thead>
<tr>
<th>Sign/Symptom</th>
<th>Children</th>
<th>Adults</th>
<th>Elderly</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cough (nonproductive)</td>
<td>++</td>
<td>++++</td>
<td>+++</td>
</tr>
<tr>
<td>Fever</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Myalgia</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Headache</td>
<td>++</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Malaise</td>
<td>+</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Sore throat</td>
<td>+</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Rhinitis/nasal congestion</td>
<td>++</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Abdominal pain/diarrhea</td>
<td>+</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>++</td>
<td>–</td>
<td>+</td>
</tr>
</tbody>
</table>

+++ Most frequent sign/symptom
+ Least frequent
– Not found

Sources:
# Age-Adjusted Incidence Ratio of Cardiovascular Events After Vaccination or Infection

<table>
<thead>
<tr>
<th>Event (count) before First MI</th>
<th>Days 1–14 (IR, n)</th>
<th>Days 15–28 (IR, n)</th>
<th>Days 29–91 (IR, n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Influenza vaccine (20,486)</td>
<td>(~0.72, 357)</td>
<td>0.73, 417</td>
<td>(~1, 2154)</td>
</tr>
<tr>
<td>Td vaccine (7,966)</td>
<td>(~1, 54)</td>
<td>(~1, 46)</td>
<td>(~1, 299)</td>
</tr>
<tr>
<td>PPSV23 vaccine (5,925)</td>
<td>(~1, 39)</td>
<td>(~1, 43)</td>
<td>(~1, 177)</td>
</tr>
<tr>
<td>SRTI (20,921)</td>
<td>(~3.8, 1020)</td>
<td>1.95, 576</td>
<td>1.4, 1658</td>
</tr>
<tr>
<td>UTI (10,448)</td>
<td>(~1.6, 233)</td>
<td>132, 217</td>
<td>1.23, 820</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Event (count) before First CVA</th>
<th>Days 1–14</th>
<th>Days 15–28</th>
<th>Days 29–91</th>
</tr>
</thead>
<tbody>
<tr>
<td>Influenza vaccine (19,063)</td>
<td>(~0.77, 365)</td>
<td>0.88, 409</td>
<td>(~1, 2051)</td>
</tr>
<tr>
<td>Td vaccine (6,155)</td>
<td>(~1, 41)</td>
<td>(~1, 40)</td>
<td>(~1, 209)</td>
</tr>
<tr>
<td>PPSV23 vaccine (4,416)</td>
<td>(~1, 38)</td>
<td>(~1, 29)</td>
<td>(~1, 160)</td>
</tr>
<tr>
<td>SRTI (22,400)</td>
<td>(~2.4, 849)</td>
<td>1.68, 561</td>
<td>1.33, 1650</td>
</tr>
<tr>
<td>UTI (14,603)</td>
<td>(~2.2, 555)</td>
<td>1.71, 445</td>
<td>1.22, 1250</td>
</tr>
</tbody>
</table>


Abbreviations: MI, myocardial infarction; CVA, cerebrovascular accident; Td, tetanus–diphtheria; PPSV23, 23-valent pneumococcal polysaccharide vaccine; SRTI, systemic respiratory tract infection; UTI, urinary tract infection.
“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 with infection
- Influenza, RSV, pneumonia
- Bladder infection, pressure sores
T-Dependent Antibody Response Following Thymic Transplant From Mice of Different Ages

Age (months) of Donor Mice

Antibody Level

Vaccine Response Declines With Age

- Influenza vaccine response declines with age
- Pneumococcal vaccine response declines with age
- Hepatitis vaccine response declines with age
- Zoster vaccine response declines with age

Less response means less protection
Immune Response Declines With Age

- **T-cell responses reduced in age**
  - Less antibody produced in response to infection
  - Lower quality antibody produced in response to infection
- **Cytokines change with age**
  - Cytokine response changes with age
    - Increased inflammation at baseline
    - Reduced pace of increase with infection
    - Much longer duration to return to baseline after infection
    - Prothrombotic state exaggerated and prolonged with age
  - **Vascular outcomes**
Summary

• Host, environmental, and viral factors account for variations in severity of infection
• Advancing age modulates symptom presentation, outcomes (such as respiratory infection vs. vascular events, duration of presentation)
• Immune senescence affects ability to respond to and clear infection, and to derive protection from vaccine
Polling Question- Follow Up

TRUE OR FALSE ABOUT RSV?

1. More serious outcomes from infectious diseases occur primarily due to advancing age?
2. Less symptomatic in oldest and youngest
3. Increases seasonal hospitalization and mortality
Preventing and Managing Respiratory Syncytial Virus Infections

David H. Canaday, MD
Division of Infectious Disease
Case Western Reserve University and Cleveland VA
## DISCLOSURE(S)

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<tr>
<th>Research Support:</th>
<th>NIH, VA, Seqirus, Merck</th>
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<tr>
<td>Consultant:</td>
<td>None</td>
</tr>
<tr>
<td>Discussion of Off-Label, Investigational, or Experimental Drug Use:</td>
<td>Multiple vaccines and drugs in development discussed</td>
</tr>
</tbody>
</table>
Overview of RSV Care

- Challenges in making a specific diagnosis
- Management of other potential pathogens
- Special conditions
  - COPD
  - Congestive heart failure
  - Immunocompromised conditions
- Use of steroids
- Use of antibiotics
Making the RSV Diagnosis

- Antigen detection less sensitive in adults because of low viral load
- Cultures grow slowly but are specific
- RT-PCR–based assay is best choice for adults who may have lower viral loads
- Serology is feasible but only useful retrospectively—results not available quickly enough and there is a titer change between acute and convalescent phases of disease
Therapeutic Options in RSV: It’s All Supportive Care

- Steroids not beneficial in older adults — only observational data, and use was associated with longer hospitalizations and more hospital-acquired bacterial infections
- Bronchodilators
- Bacterial superinfections found in 12.5% of patients with RSV — similar to those with influenza
- Antiviral measures; possibly antibiotics
- Treatment of influenza depending on their risk with >65 being a risk so all of geriatric population and clinical/diagnostic picture
  - Oseltamivir

Bacterial Superinfections

- Common in patients with RSV — occur in 12.5% of RSV+ infections
- Study of 842 winter hospitalizations showed 348 viral infections (41%); of those, 61% were viral infections alone
- RSV third most common pathogen, after influenza A and B
- 18% of RSV+ patients had confirmed bacterial superinfections in this study
- Tests for detecting bacterial superinfections: Urinary antigens for *Strep. pneumoniae*, cultures, and serum procalcitonin
- 90% of patients received antibiotics as part of treatment

Consider Antibiotics

- **Pneumococcus** most common pathogen, followed by *Haemophilus, Staphylococcus, Moraxella, Klebsiella*, others
- Strongly consider adding antibiotic coverage with any signs of pneumonia or with severe disease requiring hospitalization

Ribavirin: FDA-Approved Treatment for RSV Infections

- FDA approved for infants, young children, and special populations with RSV; no data in adults to guide use other than those with immunosuppression, transplants
- Compound is guanosine analog that interrupts RNA synthesis
- Can be used orally or inhaled
- No consensus for ribavirin exists even in the high-risk transplant population where it is used commonly
FDA-Approved Antibody for RSV Prevention in Pediatrics

- Palivizumab is anti-RSV humanized monoclonal antibody approved by FDA only in children for RSV prevention — not treatment
- Used primarily in infants
- Some data support use in immunosuppressed patients as single agent or in combination with ribavirin and/or steroids
Prevention of RSV: CDC’s view

Facts
• Multiple adult outbreaks on bone marrow transplant and oncology units. Visitors and health care workers are main source of RSV.
• RSV can survive several hours on hands and fomites
• 42% of infected persons are asymptomatic; shedding can occur for an average 11 days

Recommendations
• Handwashing and droplet precautions (glove, mask, eye protection) are key hospital-based measures
• Isolation in private room or RSV cohorting (including cohort nursing staff)
• Limit movement of patients; if moved, require wearing of masks
• Restrict care by health care workers with upper respiratory symptoms during RSV season when possible
RSV Treatments in Development

- Presatovir (Gilead GS-5806) — oral entry inhibitor had challenge study with reduction in symptoms and viral load in adults
  - A Phase 2b, Randomized, Double-Blind, Placebo-Controlled Multi-Center Study Evaluating Antiviral Effects, Pharmacokinetics, Safety, and Tolerability of GS-5806 in Hospitalized Adults With Respiratory Syncytial Virus (RSV) Infection
- ALS-008176 nucleoside analogue with promising results in RSV challenge study
- ALX-0171 nanobody therapy to block RSV fusion to cells. Phase 2 trial in infants ongoing
RSV: Would a Vaccine Work?

• Studies with a formalin-inactivated, virus-based vaccine in 1960s showed potentiation of disease in vaccine recipients
• Older adults with lower anti-RSV titers are more likely to develop severe disease
• Patients can be infected with RSV more than once in a season but second time milder
• Suggestion that CD8 cells important in viral control and diminished response with aging
• RSV is RNA virus, which means replication is error prone; vaccine is likely to lose efficacy over time and require adjustment
• RSV F is most common target
• F-protein, a highly conserved amino acid sequence called antigenic site II involved in virus binding and fusion for infection
• Palivizumab, which also targets antigenic site II, has demonstrated protection in several randomized clinical trials to have protection
# RSV Vaccines in Development

## RSV Vaccine and mAb Snapshot

<table>
<thead>
<tr>
<th>TECHNOLOGY</th>
<th>PHASE 1</th>
<th>PHASE 2</th>
<th>PHASE 3</th>
<th>MARKET APPROVED</th>
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<tbody>
<tr>
<td><strong>WHOLE INACTIVATED</strong></td>
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<tr>
<td><strong>PARTICLE-BASED</strong></td>
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<tr>
<td><strong>SUBUNIT</strong></td>
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<tr>
<td><strong>NUCLEIC ACID</strong></td>
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<tr>
<td><strong>GENE-BASED VECTORS</strong></td>
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<tr>
<td><strong>COMBINATION/IMMUNO-PROPHYLAXIS</strong></td>
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**PRECLINICAL**

- **Antigen**: Preclinical
- **mAb**: Preclinical
- **Vaccine Development**: Preclinical
- **Target Indication**: Preclinical

**TARGET INDICATION**: F = Pediatric; M = Maternal; E = Elderly; T = TID

**UPATED SEPTEMBER 23, 2016**


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[geron.org](http://geron.org) #RSV @geronsociety
RSV Vaccines in Phase 2 or 3 Trials

• One product linked to RSV-F nanoparticles
  o Recent disappointing phase 3 trial of nonadjuvanted vaccine in older adults
  o Phase 3 trial of RSV-F nanoparticles with alum in pregnant women
  o Phase 2 study will have the prior candidate +/- alum or a novel adjuvant, Matrix-M, a saponin-based adjuvant that boosts both cellular and humoral immunity

• Another product is recombinant pre-RSV-F subunit vaccine +/- adjuvant; is in phase 2 trials with focus on infants and pregnant women

• A third product, MVA-BN RSV vaccine, has both surface proteins (G and F); is on an attenuated smallpox vaccine platform with a goal of producing strong antibody and T-cell responses
Questions?

Supported by Novavax

GSA

• The nation's oldest and largest interdisciplinary organization devoted to research, education, and practice in the field of aging
  – 5,500+ interdisciplinary members around the world touching all facets of aging

• Mission
  – Promote multidisciplinary and interdisciplinary research in aging
  – Translate and disseminate research findings
  – Promote/advocate for education/awareness on aging across disciplines
  – Foster application of research into policy development

• To view other GSA webinars visit geron.org/webinar

• Email navp@geron.org with additional questions
Thank you!
Questions and Discussion

Emailed to attendees following the webinar:
• Webinar PowerPoint
• Webinar recording
In an effort for continual improvement, we would like to hear your thoughts. Please provide feedback by clicking the survey link, which will be emailed to you at the end of the webinar.

Thank you again and we hope you enjoyed the program!