Respiratory Syncytial Virus (RSV) and RSV Vaccines

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Respiratory Syncytial Virus (RSV) in Infants and Young Children

- **Common cause of acute respiratory infections (ARI)**
  - 50% infected in 1st year of life
  - Virtually all children infected by 2 years of age
- **Most common cause of lower respiratory tract infections (LRTI) among infants**
  - Manifests as bronchiolitis or pneumonia
- **Can present with apnea in infants <6 weeks of age**
- **Questionable relationship between RSV infection during early childhood and subsequent development of reactive airway disease, wheezing**

RSV in Adults

- **Repeat infections affect adults**
- **Most often upper respiratory tract illnesses**
  - Symptoms often more severe than common cold
  - Less fever and fewer systemic symptoms compared to influenza
- **Lower respiratory tract illnesses can occur**
  - Especially among immunocompromised, underlying cardiopulmonary disease, elderly

Symptoms in Adults ≥65 Years

Table 6. Frequency of Symptoms Among Single Virus Infections (Viruses Detected in at Least 30 Cases)

No. of Episodes (N)	RSV (N = 39)		Influenza A (N = 98)		Metapneumovirus (N = 31)		Rhinovirus/ Enterovirus (N = 75)		Coronavirus (N = 30)	
Symptom	n[a]	% (95% CI)	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)
Nasal congestion	28	71.8 (55.1–85.0)	76	77.6 (68.0–85.4)	23	74.2 (55.4–88.1)	58	77.3 (66.2–86.2)	28	93.3 (77.9–99.2)
Sore throat	25	64.1 (47.2–78.8)	63	64.3 (54.0–73.7)	20	64.5 (45.4–80.8)	58	77.3 (66.2–86.2)	22	73.3 (54.1–87.7)
New or worsening cough	36	92.3 (79.1–98.4)	87	88.8 (80.8–94.3)	28	90.3 (74.2–98.0)	61	81.3 (70.7–89.4)	27	90.0 (73.5–97.9)
New or worsening dyspnea	20	51.3 (34.8–67.6)	32	32.7 (23.5–42.9)	8	25.8 (11.9–44.6)	26	34.7 (24.0–46.5)	9	30.0 (14.7–49.4)
New or worsening sputum production	27	69.2 (52.4–83.0)	49	50.0 (39.7–60.3)	14	45.2 (27.3–64.0)	33	44.0 (32.5–55.9)	12	40.0 (22.7–59.4)
New or worsening wheezing	18	46.2 (30.1–62.8)	30	30.6 (21.7–40.7)	3	9.7 (2.0–25.8)	11	14.7 (7.6–24.7)	8	26.7 (12.3–45.9)
Fever	22	56.4 (39.6–72.2)	71	72.4 (62.5–81.0)	17	54.8 (36.0–72.7)	30	40.0 (28.9–52.0)	15	50.0 (31.3–68.7)
Headache	32	82.1 (66.5–92.5)	72	73.5 (63.6–81.9)	25	80.6 (62.5–92.5)	57	76.0 (64.7–85.1)	26	86.7 (69.3–96.2)
Fatigue	31	79.5 (63.5–90.7)	75	76.5 (66.9–84.5)	21	67.7 (48.6–83.3)	59	78.7 (67.7–87.3)	20	66.7 (47.2–82.7)
Myalgia	25	64.1 (47.2–78.8)	69	70.4 (60.3–79.2)	19	61.3 (42.2–78.2)	51	68.0 (56.2–78.3)	23	76.7 (57.7–90.1)
Feverishness	18	46.2 (30.1–62.8)	58	59.2 (48.8–69.0)	18	58.1 (39.1–75.5)	36	48.0 (36.3–59.8)	17	56.7 (37.4–74.5)

Abbreviations: CI, confidence interval; RSV, respiratory syncytial virus.

[a] n, number of subjects in a given category.

Falsey et al., JID 2014; 1873–81.

Burden of RSV in Older US Adults (1)

- **Importance first recognized with outbreaks in care facilities for older adults**

- **~177,000 hospitalizations annually**
- **~14,000 deaths annually**

- **Average annual RSV hospitalization rate of 15 per 10,000 residents**
  - Prospective study over 3 winter seasons
  - 1 county (Davidson County, Nashville, TN)
  - Similar hospitalization rate for influenza

Falsey 2005; Widmer 2012

Burden of RSV in Older US Adults (2)

- **154 medically attended RSV episodes per 10,000 persons ≥50 years**
  - Prospective study over 4 respiratory seasons seeking care for ARI
  - Increasing incidence with age

- **In adults ≥65 years with chronic lung disease:**
  - Retrospective cohort using TN Medicaid data
  - 17.7 hospitalizations per 1,000 persons
  - 4.7 deaths per 1,000 persons

McClure 2014; Griffin 2003

Etiology and Transmission

- **Enveloped RNA Paramyxoviridae virus**
  - 2 major subgroups: A and B
  - 10 genes that encode 11 proteins
    - F and G: induce neutralizing antibody
    - F highly conserved; vaccine target
- **Humans only source of transmission**
- **Spread by direct or close contact**
  - Large droplets or fomites on objects/surfaces
- **Incubation period: 4–6 days (range 2–8 days)**
- **Viral shedding: 3–8 days (up to 4 weeks)**

Laboratory Testing

- **Rapid tests of respiratory specimens (midturbinate, nasal swab or wash)**
  - Antigen assays
    - High sensitivity in young children (80–95%)
    - Lower sensitivity (14–39%) in adults due to low virus shedding
  - Reverse transcriptase-polymerase chain reaction (RT-PCR) assays
    - Higher sensitivity in adults (>90%)
- **Viral isolation from respiratory specimens in cell culture**
  - Can take 1–5 days
  - Expensive and less sensitive
- **Serology for seroprevalence studies**
  - Can add to case finding in adults

Goal for RSV Vaccine Development

- **Safely induce sufficient immunity to protect against serious RSV infections (e.g. lower respiratory tract infection, possibly apnea in infants)**
  - Induction of sterilizing immunity is not required (and might not be feasible)

Formalin Inactivated Vaccine Trials (1966–1967)

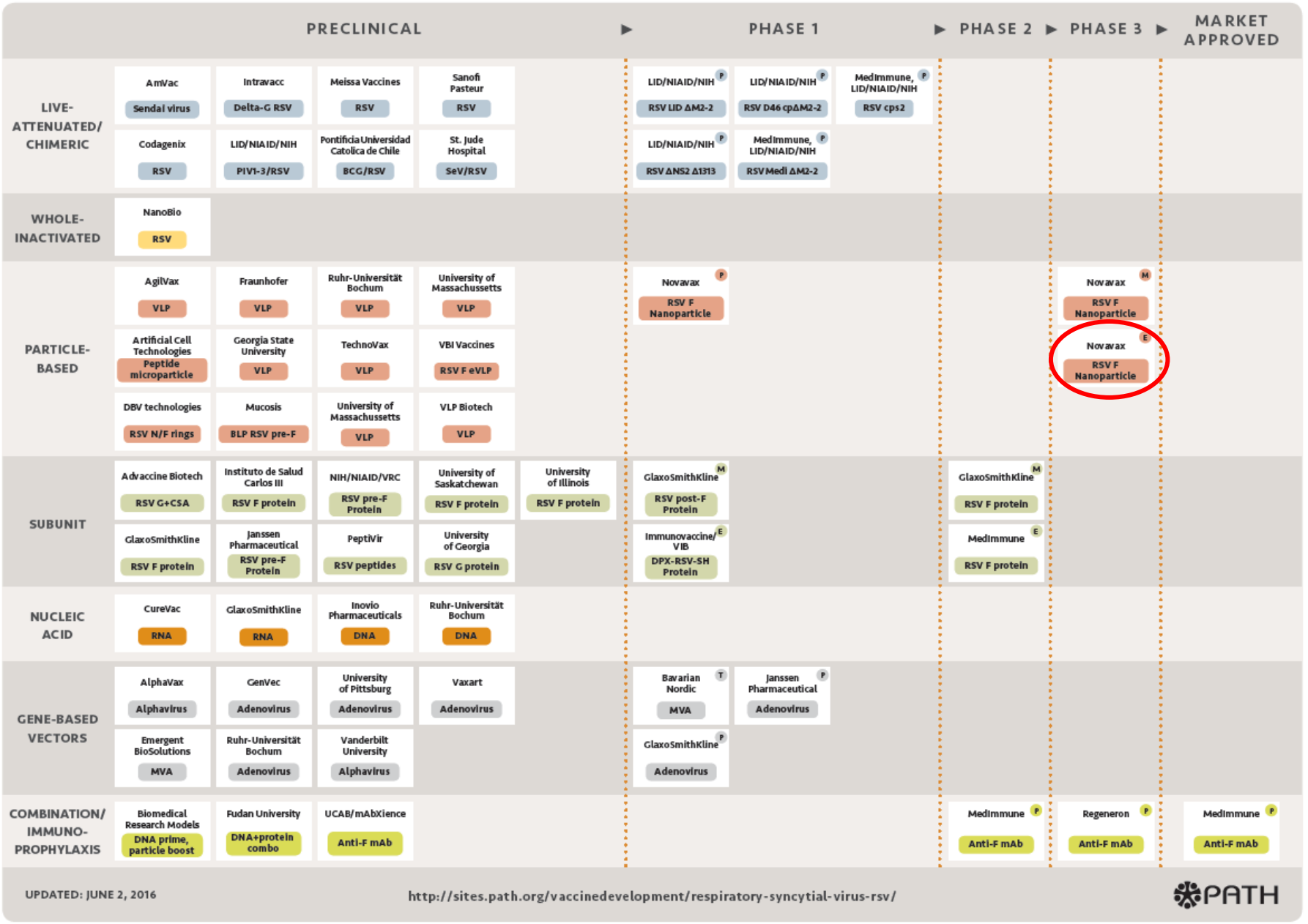
- **Children 2 months–7 years**
- **Seronegative vaccine recipients had more severe RSV-associated LRTIs than non-recipients when infected with RSV**
  - 80% recipients hospitalized vs. 5% controls
  - 2 deaths in vaccine group
- **Caused vaccine-enhanced disease syndrome in RSV-naïve infants (i.e. those that had not yet had primary infection)**

Implications of the Formalin-Inactivated Vaccine Trials

- **Because of enhanced disease, non-replicating vaccines unlikely to be used in RSV-naïve infants**
- **Therefore, different vaccines for different target populations**
  - Replicating or vectored vaccines for active immunization of RSV-naïve infants and children
  - Subunit (RSV F) vaccines with or without adjuvant for maternal immunization to protect the very youngest infants
  - Subunit (RSV F) vaccines with or without adjuvant to protect the elderly

RSV Vaccine and mAb Snapshot

TARGET INDICATION: (P) = PEDIATRIC (M) = MATERNAL (E) = ELDERLY (T) = TBD



UPDATED: JUNE 2, 2016

http://sites.path.org/vaccinedevelopment/respiratory-syncytial-virus-rsv/

PATH

RSV Vaccine Priority Groups: Populations at Risk of Severe Disease

- Neonates and young infants
- Older infants and children
- Pregnant women
- Older adults

Neonates and Young Infants

- Greatest potential benefit due to disease burden
- Immature immune system
- Active immunization in this age group is challenging due to pre-existing maternal antibody

- Most promising strategy for the youngest infants is maternal vaccination or administration of extended half-life mAb

Older Infants and Children

- **Issues similar to young infants, but more mature immune system and lower levels of maternally acquired antibodies**
  - Should lead to better response to vaccines
- **Development focusing on live-attenuated virus and vectored vaccines**
- **Several vaccine candidates in phase 1 clinical trials**

Pregnant Women

- **Objectives:**
  - Protect young infant by inducing high levels of neutralizing antibodies that are transferred to fetus
  - Prevent maternal to infant transmission of infection
  - Protect the pregnant woman from infection
- **Pregnant women would not be at risk for enhanced disease**

- **RSV F subunit vaccines in development**
- **Vaccine candidates in phase 1–3 clinical trials**

Older Adults

- **Substantial disease in this population**
- **Immunosenescence**

- **Subunit vaccines in development**
- **Vaccine candidates in phase 1–3 trials**
  - RSV F subunit nanoparticle vaccine will be the first RSV vaccine to be considered for FDA licensure and use, and the focus of the current ACIP RSV WG

Adult RSV Vaccine to Come

- In August 2015, news media reported early indications of vaccine efficacy for the Novavax vaccine targeted for older adults. More data will be forthcoming as phase 3 trial results become available, and these will be presented to ACIP.

Considerations for RSV Vaccine in Older Adults

- Disease burden
- Outcome measures
- Immunogenicity and correlates of protection
- Duration of protection
- Cost-effectiveness
- Implementation
- Education of stakeholders

Proposed ACIP Timeline and Activities

- 2016: Epidemiology and burden of RSV in older adults
- 2017: Vaccine manufacturer presents results, correlates of protection and immunogenicity, cost-effectiveness
- 2018: Implementation considerations, GRADE, potential vote

Thank You

For more information please contact Centers for Disease Control and Prevention

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