RSV Trends, Treatments and Future possibilities

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Disclosure Statement

- Terry Laurila has no relevant financial relationship(s) with ineligible companies to disclose.

  and

- None of the planners for this activity have relevant financial relationships with ineligible companies to disclose.

Learning Objectives

At the completion of this activity, the participant will be able to:

- 1. explain the changes in respiratory syncytial virus (RSV) seasonality
- 2. discuss how the investigational monoclonal antibodies differ from Palivizumab
- 3. define how an RSV Vaccine could fit into the RSV prophylactic treatment regimen.

Pretest Question 1

- RSV infection rates present in well defined seasons that begin in late fall and end in the spring usually November through March.
- True or False

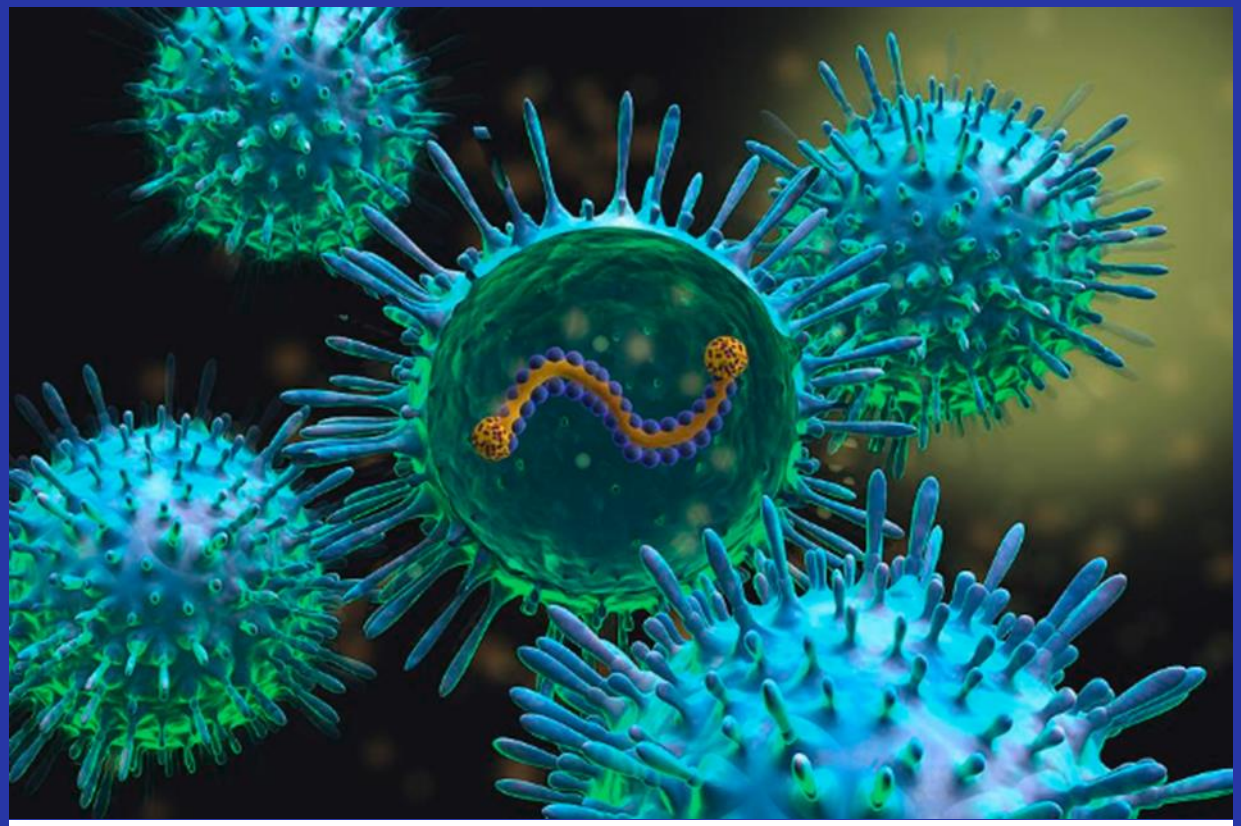
Pretest Question 2

- Which statements about Nirsevimab are true?
- A. Nirsevimab has an extended half life 59.3 days
- B. Nirsevimab is a one-time intramuscular dose
- C. Nirsevimab will be indicated for all infants entering their first RSV season
- D. All the above

Pretest Question 3

- RSV Vaccines voted safe and effective by the FDA advisory panel employ what target strategy ?
- A. Target the pre Fusion (F) glycoprotein
- B. Target the attachment (G) glycoprotein
- C . Use live-attenuated virus
- D. Use inactivated virus

Respiratory Syncytial Virus



Human Respiratory Syncytial Virus is a photograph by Ella Maru Studio / Science Photo Library which was uploaded on September 16th, 2018.

RSV Facts

- RSV discovered in 1956 is a common respiratory virus that causes cold like symptoms in all age groups.
- In the USA 2.1 million outpatient visits for children < 5 years old
- 58,000 to 80,000 hospitalizations USA each year among children younger than 5 years old
- Leading cause of hospitalization in children <1 year of age
- 2 out of 3 babies get RSV by age 1
- 100 – 300 deaths in children younger than 5 years old
- RSV infects virtually all children by age 2 years

RSV Facts

- In USA 60,000 to 160,000 hospitalizations each year among adults 65 years and older
- 6,000 to 14,000 deaths in USA among over 65 years and older
- Exacerbate other underlying conditions
  - Asthma, COPD, Acute myocardial infarction, stroke and long term decline of respiratory function.
- Globally RSV estimated 64 million people and causes 160,000 deaths each year

RSV transmission

- Primarily spread by respiratory droplets
  - Infected person coughs or sneezes
  - Virus droplets in your eyes, nose or mouth
- Secondary transmission direct contact
  - Kissing the face of a child
- Individual touches face after direct contact with contaminated surface like a doorknob
- RSV Infected people contagious for 3 to 8 days
- Those with weakened immune systems can be contagious for up to 4 weeks

RSV Transmission Prevention

- Wash hands often
- Keep hands away from face
- Avoid close contact with sick people
- Cover coughs and sneezes (tissue or upper shirt sleeve)
- Clean and disinfect surfaces
- Stay at home when sick

RSV Infection symptoms

- Early in children: runny nose, decrease appetite, sneezing, cough progressing to wheezing or difficulty breathing
- Fever may or may not always occur
- In less than 6 month olds: irritability, decrease activity, decrease appetite, apnea (breathing pauses more than 10 seconds)
- Severe illness Bronchiolitis or pneumonia

RSV in Infant and Young Children

- Dangerous for
  - Premature infants
  - Infants 6 months or younger
  - Children under 2 years with chronic lung disease or congenital heart disease
  - Children with weakened immune system
  - Children with neuromuscular disorders

    difficulty swallowing or clearing mucus secretions

RSV in Adults

- Symptoms similar to cold or flu
  - Fever
  - Congestion
  - Cough
  - Sore throat
  - Irritability
  - Tiredness
  - Runny nose
  - Wheezing
  - Headache

  Usually lasts less than 5 days

  Some may have more severe symptoms

  Some may notice no symptoms

High risk adult severe symptoms

- High risk are older adults 65 years or older
- Chronic lung or heart disease
- Weakened immune systems
- RSV exacerbation of other conditions
  - Asthma
  - Chronic Obstructive Pulmonary Disease
  - Congestive Heart disease

RSV diagnosing & testing

- Physical examination followed by laboratory tests
- Nasal Aspirate, Nasal wash or nasopharyngeal swab
- Rapid Antigen testing
  - Rapid tests of samples with results in 15 minutes
  - Three steps with two color results
  - Some tests more steps
  - Internal and external controls included
- RSV RT-PCR
  - Reverse Transcription Polymerase Chain reaction
- Viral Culture

Care for mild RSV infection

- Most RSV infections resolve in a week or two
- Manage fever and pain with acetaminophen or ibuprofen
- Hydration- drink enough fluids
- Talk to your healthcare provider before giving non-prescription medicines

Severe RSV Infection

- 1 to 2 percent of children younger than 6 months of age with RSV infection need hospitalization
- Severe RSV is the leading cause of hospitalization for children less than 1 year of age in the US.
- Oxygen, IV fluids, mechanical ventilation
- Most will improve and are discharged in a few days

RSV Seasonality

Measure by percent positive RSV cultures

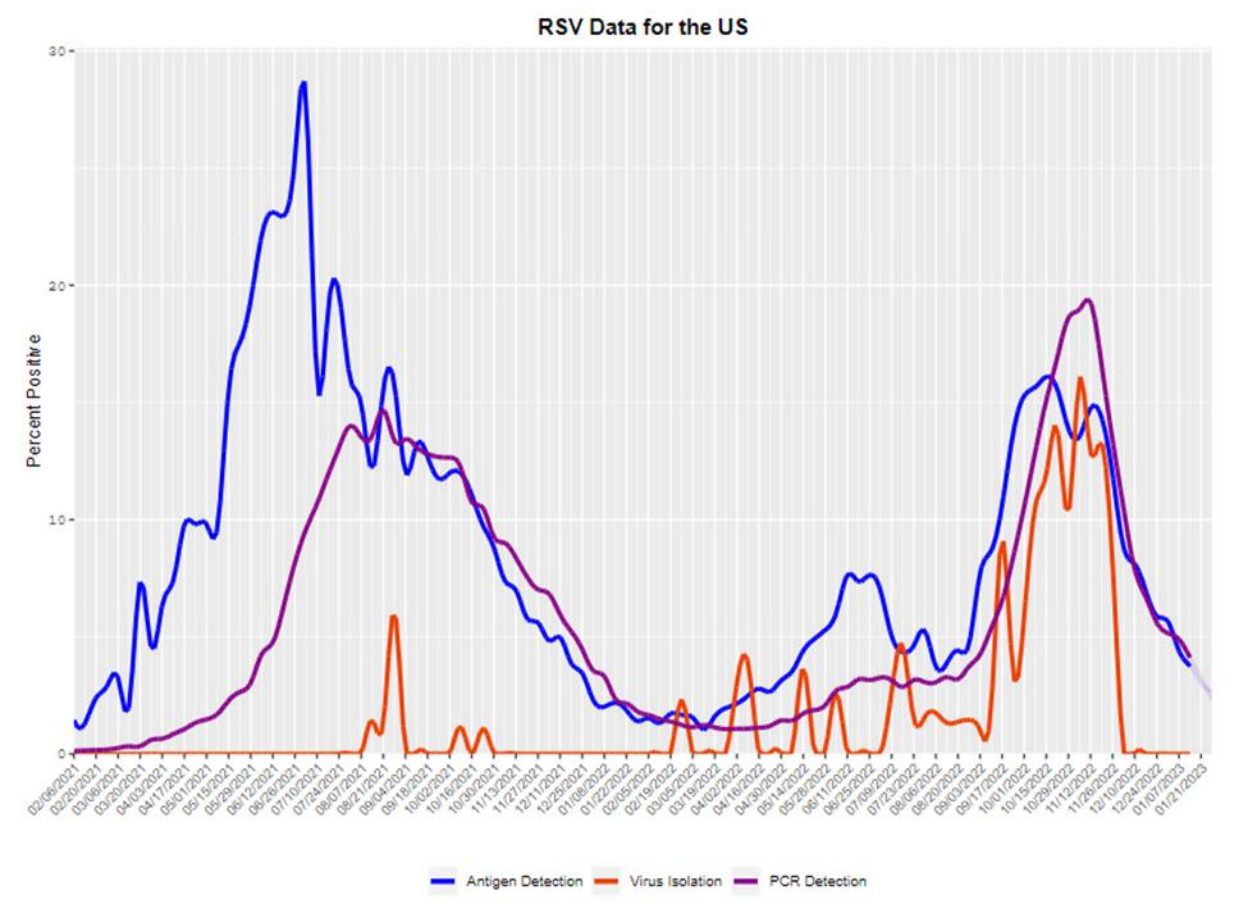
PRE COVID before 2020

- RSV Season in Ohio started Mid September to November and ends in March to April
- Areas nearer to equator start sooner and ends later
  - Florida and Hawaii

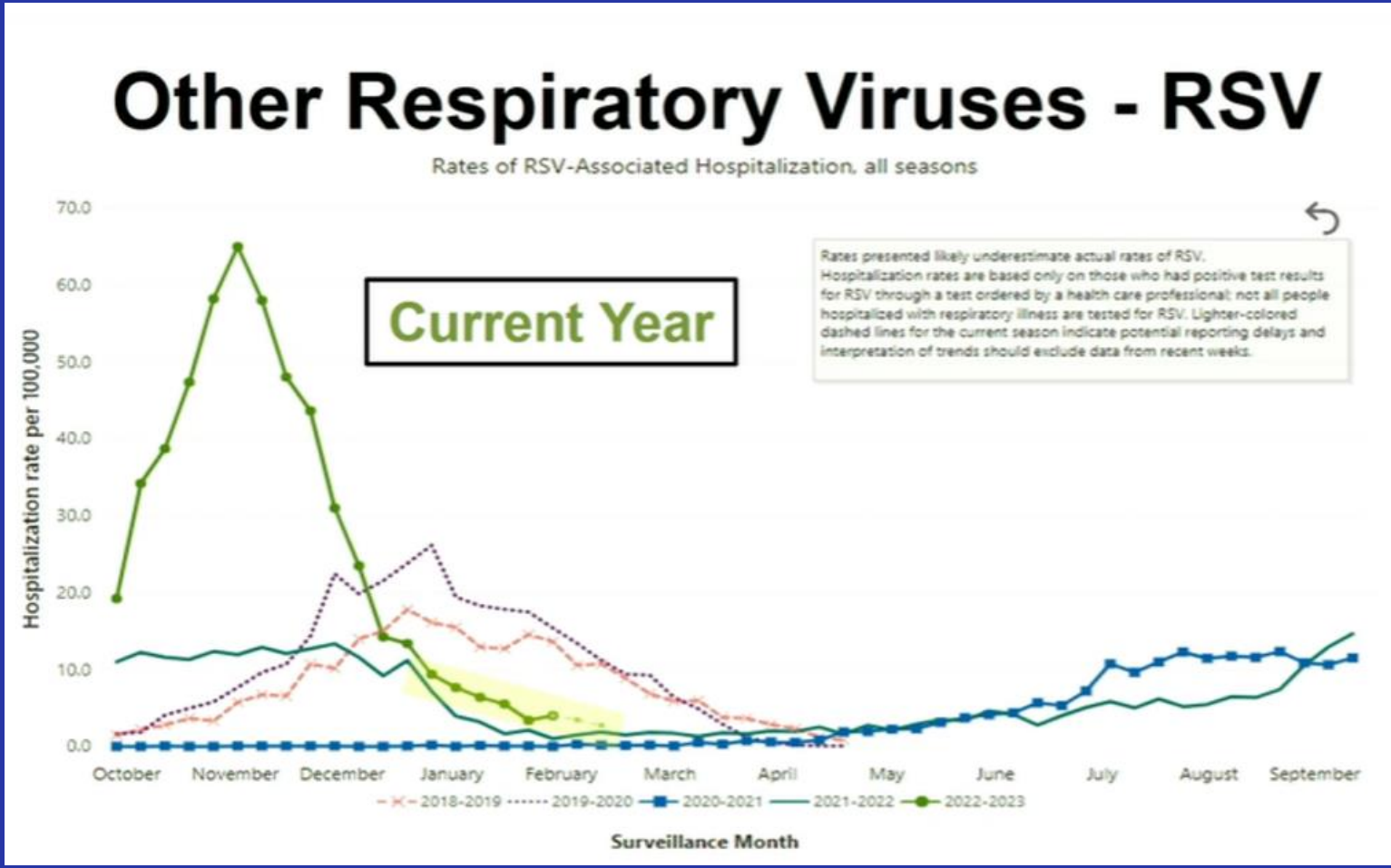
POST COVID after 2020

- Onset April and May of 2021 through end of 2021
- Next season September 2022 to Beginning of February 2023
- Each State may have its own trend and season in that State

Recent RSV seasonality



RSV associated Hospitalizations



Antiviral medications

- Ribavirin (6 gram for inhalation solution)
- Inhaled oral or inhaled nasal
- AAP guidelines: select hospitalized infants or small children with life-threatening RSV lower respiratory tract infections.
- Routine use for RSV is not recommended.
- Rapid RSV test either prior to starting or within 24 hours
- Commercially available nasal and oral inhalation use a small particle aerosol generator available from the manufacturer
- Use in adults for RSV is not recommended per the manufacturer
- Table 2 NIOSH hazardous drug developmental and/or reproductive hazard

RSV MAB - Palivizumab

- Palivizumab - Antiviral Monoclonal antibodies to RSV fusion protein for passive immunity
- Indicated for premature infants born <36 wGA
- Children with Bronchopulmonary dysplasia /Chronic Lung Disease of Prematurity < 25 months
- Children with Hemodynamically significant congenital Heart disease <25 months
- Start a 5 dose regimen at start of RSV season
- 15 mg/kg intramuscular injection every 28 days
- Half life 24.5 days
- AAP Guidelines

Suptavumab

- REGN2222 Suptavumab by Regeneron
- Aug. 14, 2017 /PRNewswire/ -- Regeneron Pharmaceuticals, Inc. (NASDAQ: REGN) today announced that a Phase 3 study evaluating suptavumab (REGN2222), an antibody to respiratory syncytial virus (RSV), did not meet its primary endpoint of preventing medically-attended RSV infections in infants. Suptavumab did show signs of efficacy in a subgroup of patients. Adverse events were generally balanced between suptavumab and placebo. Regeneron plans to discontinue further clinical development of this antibody.
- Clinical Infectious Disease Vol 73, Issue 11, 1 Dec 20021 4400-4408 Suptavumab for prevention of Mediclly attened respiratory syncytial virus infection in preterm infacnts.

Extended Half life RSV MAB
Motavizumab

- Motavizumab differed from palivizumab by 13 amino acids
- In vitro 20-fold more potent
- June 2010 FDA antiviral drug advisory committee declined to endorse
- When compared to palivizumab do not gave evidence of superiority in terms of efficacy
- AstraZeneca discontinued development

Extended Half life RSV MAB
Clesrovimab

- MK-1654 Merck
- Phase 3 trials in process to evaluate the safety, efficacy and pharmacokinetics of MK-1654 in infants and children at increased risk for severe RSV disease.
- Comparing to palivizumab in studies
- Single dose IM Injection
- No data results yet

- Clincal trials.gov/ct2/show/study/NTC0493880

Extended Half life RSV MAB Nirsevimab

- Nirsevimab by Astra-Zeneca - Sanofi
- 74.5% efficacy against RSV infections requiring Medical care
- Investigated as single dose passive immunization for infacnt entering first RSV season
- Phase 2/3 MEDLEY trials Showed similar safety and tolerability compared to palivizumab
- MEDLEY and MELODY trial results looked for evidence for Nirsevimab to provide RSV protection to protect congenital heart disease or chronic lung disease infants in first and second RSV seasons, as well all infants for their first RSV season.

Nirsevimab

- Nirsevimab is a recombinant IgG1Kappa monoclonal antibody targeting the RSV fusion protein
- Extended Half life mean of 59.3 days
- Dose during study 50mg <5kg and 100 mg > 5 kg
- Number-needed-to-treat analysis
  - 12 health infants treated to prevent one medically attended RSV lower respiratory infection
  - 53 healthy infants treated to prevent one RSV related hospitalization

Would be first broadly protective option against RSV designed for all infants: healthy and preterm

Nirsevimab continued

- February 2019 US FDA granted “Breakthrough Therapy Designation”
- January 2021 Nirsevimab received “Promising Innovative Medicaine designation” from the UK and “Breakthrough Therapy designation” by China center for drug Evaluation.
- Approved in Europe December 2022
- FDA approval expected summer 2023

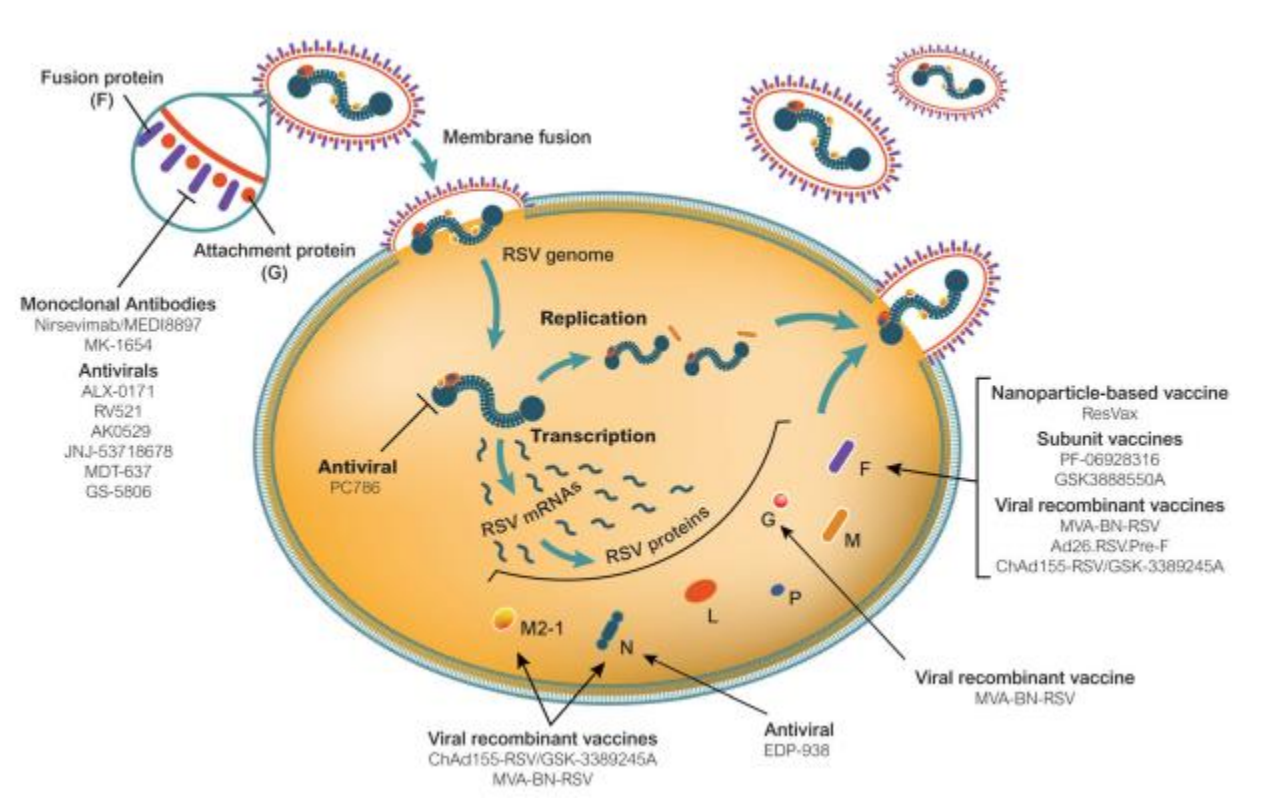
Nirsevimab

- Economic impact significant
- 3.7 million children born in US annually
- Depending on patient population could be immediate blockbuster drug?

RSV vaccine development

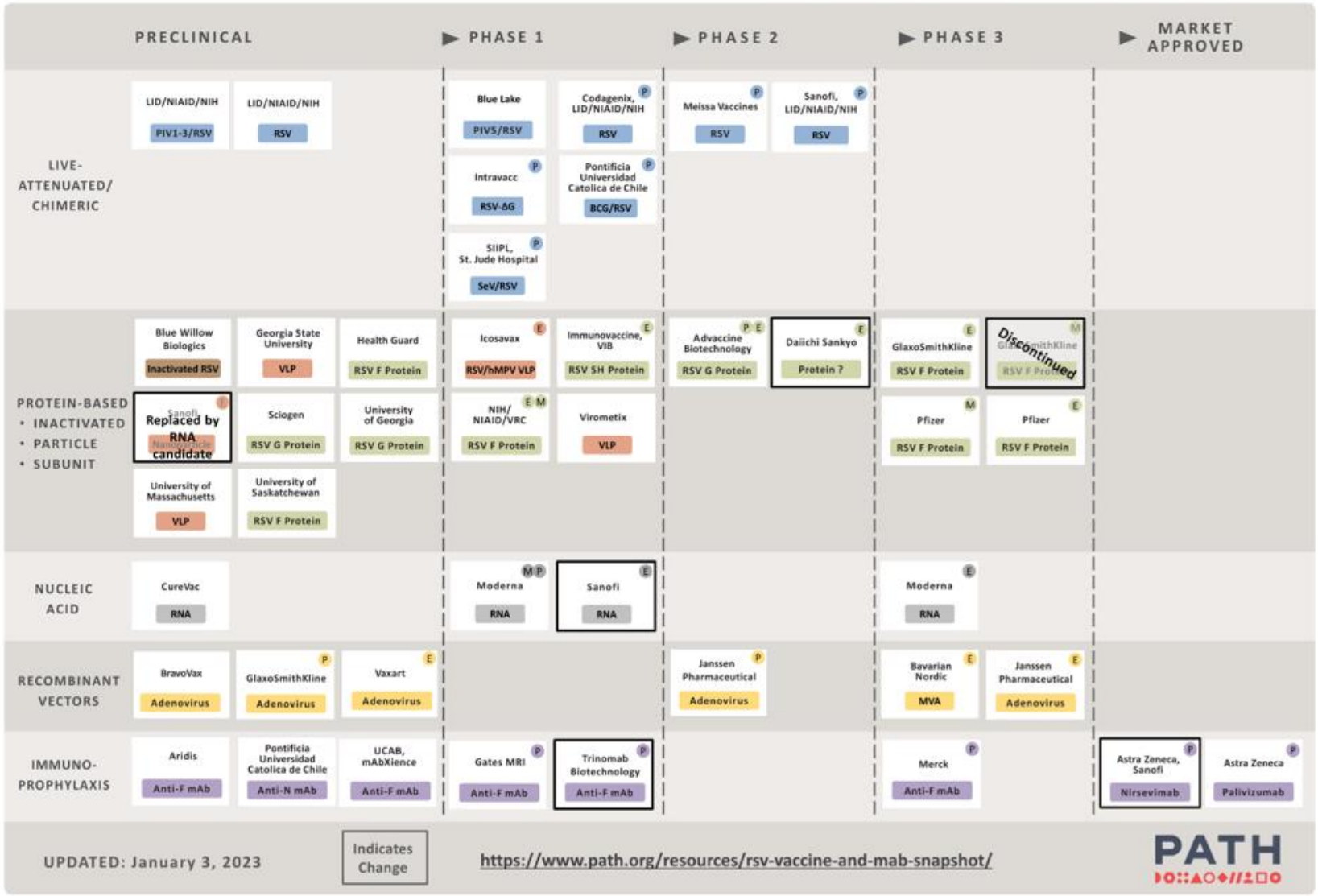
- 1966 RSV Vaccine failure
- No RSV Protection
- Some worse course of infection
- two toddler deaths.
- One hypothesis about why failed points to formalin that killed and deformed the virus
- Another hypothesis suggested that Toll-like Receptor (TLR) agonist adjuvant could boost affinity maturation so that there would be no enhanced disease symptoms that marked the 1966 failure.

RSV Vaccine development



RSV Vaccine and mAb Snapshot

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



UPDATED: January 3, 2023

Indicates Change

https://www.path.org/resources/rsv-vaccine-and-mab-snapshot/

PATH

Vaccine approaches

- 5 different approaches to a RSV vaccine
- Particle based vaccines
- Vector based vaccines
- Live-attenuated or chimeric vaccines
- Subunit vaccines
- mRNA vaccines

RSV Proteins F & G

- F: Fusion glycoprotein
  - Essential for viral entry
  - Highly conserved between RSV-A and RSV-B
- G: Attachment glycoprotein
  - Targets ciliated cells of airways
  - Variable between RSV-A and RSV-B

Vaccine approval Process

- Vaccine for RSV breakthrough Designation
- FDA Action dates
- FDA Advisory Panel
- FDA approval
- CDC Control and Prevention recommendation for use.
- Available to public

RSV Vaccine in older adults

- GSK Vaccine for older adults
- RSVPre3-AS01E brand Arexvy
- 3-1-2023 FDA advisory Panel voted 10-2 vaccine safe
- 3-1-2023 unanimously voted vaccine is effective
- Some panel members had concerns about nervous system disorders like Guillain-Barre syndrome
- Vaccine is 83% effective in preventing disease in the lower lungs of adults 60 and older
- May be more protective 94% for severe RSV disease in those over 70 and those with underlying medical conditions.
- FDA decision possible May 3, 2023

Pfizer RSVpreF -06928316
For older adult and maternal indications

- Vaccine targets the prefusion F, a fusion protein that RSV uses to enter human cells.
- Bivalent vaccine candidate equal recombinant RSV Prefusion F form subgroups A and B
- Phase 3 MATISSE trial: MATernal Immunbization Study for Safety and Efficacy.
- European medicines Agency recently accepted the RSV vaccine under marketing Authorization Application for both older adults and maternal immunization final decision second half 2023

Adult RSV Vaccine
Pfizer RSVpreF -06928316

- Targeted indication Active immunization to prevent RSV-associated LRTI in adults 60 years of age or older.
- 2-28-2023 FDA advisory panel voted 7 to 4 safe and effective for people 60 and older.
- 85% effective at preventing severe disease
- Two cases of Guillain-Barre syndrome out of 20,000 getting the Pfizer vaccine

RSV vaccine Maternal
Pfizer RSVpreF PF-06928316

- Target indication Immunize pregnant women to prevent RSV-associated LRTI in infants from birth through 6 months of age.
- Vaccine efficacy 81.8 % observed against severe medically attended lower respiratory tract infections due to RSV in infants from birth through the first 90 days of life
- high efficacy of 69,4% demonstrated through the first six months of life
- FDA Breakthrough designation March 2022
- FDA set action date August 2023

RSV Vaccine in older adults

- Moderna
- Vaccine 83,7 % effective preventing lower respiratory tract disease defined as two or more symptoms in people 60 and older
- 82,4% effective preventing lower respiratory tract disease with three or more symptoms.
- Safety and efficacy to be published in peer reviewed journal soon according to the company.
- Plans to file FDA application within first half 2023

RSV Vaccine trial Maternal

- GSK trial halted 2/18/2022 for pregnant persons
- The company “paused a late-stage trial dubbed “GRACE” as well as two other studies, based on the safety recommendations from an independent committee but did not give further details on what prompted the recommendations.”
- Vaccines for pregnant women and meant to get newborns through their first RSV season as maternal antibodies cross the placenta and are passed to the baby in the third trimester but preemies may not be protected,

RSV Vaccine in older adults

- Janssen announced December 2021 RSV vaccine for older adults appears to be 70 to 80% effective in older adults
- No current update on Janssen vaccine.

RSV Vaccines Infants

- In development but too early to note.
- Vaccine safety
- Vaccine Hesitancy

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Questions

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Need More Information?

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