Topics for Review

- Vaccine development update
- RSV consultations: WHO and NIH/FDA (Spring 2015)
- RSV Mortality & Asthma Symposium (July 2015)
RSV Vaccine Snapshot 2014

(n=51; 8 clinical)

**Preclinical**

- **Live-Attenuated**
  - Codagenix
  - EMORY University
- **Whole-Inactivated**
  - NanoBio
  - Agilvax
  - Fraunhofer
  - Georgia State University
- **Particle-based**
  - Mucosis
  - Takeda Vaccines
  - EMORY University
  - cVp Tech
- **Subunit**
  - DPX-RSV
  - Instituto de Salud Carlos III
  - Novartis
  - Renapty
- **Nucleic Acid**
  - CLIPhavoX
  - Bavarian Nordic
  - Emergent BioSolutions
- **Gene-based Vectors**
  - Crucell
  - RenuHui Biopharma
  - University of Pittsburgh
- **Combination**
  - BRM
  - Fudan University

**Phase 1**

- MedImmune
  - NH/NAID/LID
- RSV A552 a1313
- Medi-559, RSV
- RSV F Nanoparticle

**Phase 2**

- University of Illinois
- University of Saskatchewan
- MedImmune
- Novartis

**Phase 3**

- University of Korea
- Alphavirus
- Adenovirus

**Market Approved**

- RSV F protein

Updated: July 8, 2014

Source: http://www.path.org/vaccine-development/respiratory-syncytial-virus/
RSV Vaccine Snapshot

**PRECLINICAL**

- **LIVE-ATTENUATED**
  - Codagenis: RSV
  - MSD: RSV
  - Pasteur: RSV
  - St. Jude: RSV
  - Delta-G RSV

- **WHOLE-INACTIVATED**
  - NanoBio: RSV
  - AgriVax: VLP
  - Fraunhofer: VLP
  - Myxovirus: VLP
  - University of Massachusetts: VLP
  - Emory University: VLP
  - Marno: VLP
  - Technolix: VLP
  - VLP Biotech: VLP
  - Novavax: RSV F Nanoparticle

- **PARTICLE-BASED**
  - Artificial Cell Technologies: Peptide nanoparticles
  - Georgia State University: VLP
  - Ruhr University Bochum: VLP
  - University of Massachusetts: VLP
  - University of Illinois: VLP
  - University of Georgia: VLP
  - Institute of Salud Colectiva: RSV F protein

- **SUBUNIT**
  - GlassMedikkine: RSV F protein
  - Janssen Pharmaceutical: RSV F protein
  - PeptiVax: RSV F protein
  - University of Geneva: RSV F protein
  - Institute of Salud Colectiva: RSV F protein
  - University of Sao Paulo: RSV F protein
  - GlassMedikkine: RSV F protein
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- **NUCLEIC ACID**
  - CoreVax: RNA
  - GlassMedikkine: DNA
  - Innovix Pharmaceuticals: DNA
  - Ruhr-University Bochum: DNA

- **GENE-BASED VECTORS**
  - AlphaVax: Adenovirus
  - Bavarian Nordic: MVA
  - GenVec: Adenovirus
  - Ruhr-University Bochum: Adenovirus
  - Vanderbilt University: Adenovirus

- **COMBINATION/IMMUNOPROPHYLAXIS**
  - Biomedical Research Models: DNA prime- particle boosts
  - Fudan University: DNA + protein

**PHASE 1**

- MEDICINE, LEONARDO/NIH: RSV LA2

**PHASE 2**

- MEDICINE, LEONARDO/NIH: RSV LA2

**PHASE 3**

- MEDICINE, LEONARDO/NIH: RSV LA2

**MARKET APPROVED**

- MEDICINE, LEONARDO/NIH: RSV LA2

**UPDATE: JULY 10, 2015**

http://www.path.org/vaccineresources/details.php?id=1562
GSK/Okairos ChAd & MVA encoding RSV F, N & M2-1 proteins

Open label trial in 40 adults, 8 high dose and 2 low dose/group

1. PanAd3-RSV IM / MVA-RSV IM (black)
2. PanAd3-RSV IM / PanAd3-RSV IM (purple)
3. PanAd3-RSV IN / MVA-RSV IM (blue)
4. PanAd3-RSV IN / PanAd3-RSV IM (orange)

RSV MEDI ΔM2-2

- Deletion of RSV M2-2 ORF results in decreased RNA replication & increased Ag expression
- Evaluated in 15 adults, 15 RSV-seropositive children, **30 RSV-seronegative children**
- M2-2 deletion appears to ‘de-link’ virus replication and antibody response, and prime for a potent anamnestic response following natural infection with RSV
Novavax RSV F nanoparticle vaccine: preliminary efficacy results in elderly

- 1600 adults > 60 years randomized to receive 135 mcg of unadjuvanted RSV F* (n=798) or placebo (n=801)
- 4.9% attack rate (95% with RSV LRI)
- 43.9% efficacy against all RSV, 46.4% efficacy against RSV-LRI, 64% efficacy against “more severe illnesses” (not defined)

* 60 and 90 mcg doses with and without alum have been evaluated in pregnant women
MEDI8897, a RSV F mAb with extended half life

- Directed against site Ø epitope on RSV F
- YTE mutation in Fc enhances binding to the neonatal Fc receptor (FcRn) and prolongs half-life
- Goal is to administer MEDI8897 in vaccine-like fashion and with vaccine-like pricing
- Has received ‘fast-track’ designation from the FDA and is currently being evaluated in phase 1b/2a trial in healthy preterm infants (NCT02290340)
WHO consultation on RSV vaccine development: March 2015

- Provide guidance on clinical endpoints and development pathways for RSV vaccine trials with a focus on considerations of low- and middle-income countries.

- Meeting objectives:
  - Clinical development pathway for passive and active RSV immunization
  - Candidate case definitions and clinical trial endpoints

- Longer-term objectives:
  - Development of assay standards
  - RSV vaccine roadmap
  - PPC
## Strategic Goals for RSV vaccine development

1. RSV vaccines for maternal/passive immunization to prevent RSV disease in infants less than 6 months of age.

2. RSV vaccines for pediatric immunization to prevent RSV disease in infants and young children once protection afforded by maternal immunization wanes.
RSV vaccine clinical development pathway for pregnant women

- Staggered initiation in high income settings followed by LMIC
- Dosage finding primarily in non-pregnant populations
- Single dose preferred
- Concomitant administration with tetanus (LMIC) and influenza, Tdap (HIC)
- Follow-up at least 12 months; 24 months (2nd season) preferred

Clinical case definitions of severe and very severe RSV LRTI for RSV vaccine efficacy trials – LMIC focus

- Included clinical features considered to be objective, standardizable and generalizable across settings, and generally accepted markers of severity
- It was proposed that the candidate case definitions agreed upon at the meeting be piloted in ongoing and planned epidemiological studies as well as in vaccine efficacy trials
- While hypoxemia is to be assessed, the exact thresholds for hypoxemia in case definitions remain under discussion
- Acknowledgement that case definition is heavily dependent upon pulse oximetry and that standard methodologies (and possibly standardized equipment) need to be employed
An infant or young child presenting to a health facility that is part of the case ascertainment system for the phase III trial who fulfills both the laboratory **AND** clinical criteria below:

**Laboratory criterion**
RSV infection as confirmed by a fit-for-purpose, fully validated PCR assay with high specificity and sufficient sensitivity on upper respiratory samples.

**Clinical criteria**
Respiratory Infection defined as Cough or Difficulty Breathing

**AND**

LRTI defined as FAST BREATHING by WHO criteria **OR** SpO2 < 95%

**AND**

≥ 1 OF THE FOLLOWING FEATURES OF SEVERE DISEASE:

Pulse oximetry < 93%
**AND/OR** lower chest wall in-drawing

**Very Severe RSV LRTI**

An infant or young child presenting to a health facility that is part of the case ascertainment system for the phase III trial who fulfills both the laboratory **AND** clinical criteria below:

**Laboratory criterion**
RSV infection as confirmed by a fit-for-purpose, fully validated PCR assay with high specificity and sufficient sensitivity on upper respiratory samples.

**Clinical criteria**
Respiratory Infection defined as Cough or Difficulty Breathing

**AND**

LRTI defined as FAST BREATHING by WHO criteria **OR** SpO2 < 95%

**AND**

≥ 1 OF THE FOLLOWING FEATURES OF VERY SEVERE DISEASE:

Pulse oximetry < 90%
**AND/OR** Inability to feed
**AND/OR** Failure to respond/unconscious
Serology standardization and reference reagents

• RSV neutralizing antibody assays are widely used but highly variable

• Joint effort by PATH, WHO, and NIBSC to develop reference reagents and eventually to develop International Standards

• First project—comparison of results of testing a standard set of sera in 11 laboratories—has just been completed
NIH/FDA RSV vaccine workshop: June 2015

- Maternal immunization
  - Important to establish site-specific rates of prematurity, SGA, fetal loss
  - Larger safety database may be needed; will depend on frequency of adverse events to be detected; rare events may not be detected during licensure studies

- Pediatric immunization
  - Concern about adequacy of current animal models to predict safety of nonreplicating RSV vaccines in RSV-naive children

- Case definitions
  - For HIC, broader than severe or very severe RSV LRTI—any medically attended LRTI; OM as potential secondary outcome of interest; utilization of health care resources

- Long-term wheezing outcomes
  - Preliminary discussion of how/whether long-term effects on wheezing could be evaluated
  - Assumption that licensure will not be based on these long-term outcomes
Geographic settings for clinical trials

• Coordination between Northern and Southern hemisphere sites may allow for more efficient evaluation of candidate RSV vaccines.

• Substantial discussion at both the WHO mtg and NIH/FDA mtg about the need to provide data that would be clinically relevant to the countries in which vaccine is to be used, both in terms of endpoints and sufficient enrollment of comparable populations.
  • Single multicountry efficacy trial vs parallel efficacy trials in HIC and LMICs: TBD by individual sponsors.
RSV Mortality and Asthma Symposium, Buenos Aires: July 2015

- **RSV mortality**
  - Review what is currently known about RSV mortality in hospitals and in the community
  - Discuss ways in which new studies (e.g., CHAMPS) and new methodologies (e.g., minimally invasive autopsies) can improve our understanding of RSV mortality in the community

- **RSV and long-term wheezing/asthma**
  - Review what is currently known about the relationship between early RSV infection and long-term wheezing in HIC and LMIC
  - Discuss exposures particular to LMICs (e.g. smoke from biomass fuels, helminth infection) that might act as co-factors in determining long-term wheezing outcome following RSV infection
  - Discuss ways in which RSV vaccine efficacy trials might be leveraged to assess impact of prevention of early RSV disease on long-term wheezing outcomes
Challenges in planning long-term follow-up for RSV vaccine (mAb) trials

• Follow-up will occur after unblinding for primary efficacy endpoints

• Large numbers may be needed; may require pooling across studies

• Standardized outcome definitions will be needed

• Ability to measure outcomes that rely on pulmonary function testing will vary across sites
Available tools for evaluation of recurrent wheezing/asthma in children

### 36 MONTHS OF AGE: Recurrent wheezing outcome

**Potential survey instruments**
- Core asthma component from ISAAC questionnaire
- Other validated survey instruments

**Potential physiologic assessments**
- Forced oscillation technique (FOT)
- Spirometry
- Airway resistance, Interrupter technique (Rint)

### 60 MONTHS OF AGE: Asthma outcome

**Standard tools**
- Core asthma component from ISAAC questionnaire
- Other validated survey instruments
- Spirometry and test of reversibility.

**Potential tools to measure physiology and disease biomarkers**
- Forced oscillation technique (FOT)
- Airway resistance, Interrupter technique (Rint)
- Fractional exhaled Nitric Oxide (FeNO)

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