Infant RSV Program
WHO 23-24 March 2015
Agenda

- Replication-competent intranasal RSV vaccines
  - Live attenuated *ts ca* intranasal RSV vaccine
  - b/hPIV3 Vectored subunit intranasal vaccine

- Case definition for Lower Respiratory Tract Illness
  - Diagnosis based case definition
  - Objective criteria based case definition

- Passive infant vaccination with mAb
  - Approaches for seasonal administration
  - Approaches for birth-dose administration
Vaccine program with replication-competent constructs

- **MEDI-559**: live attenuated intranasal vaccine
  - Construct: Multiple point mutations in RSV virus
  - Attenuation: temperature sensitive, cold-adapted
  - Study CP-147: 5-24mo seronegative in USA (N=120)

- **MEDI-534**: live vectored intranasal vaccine
  - Construct: RSV F engineered into bovine:human PIV3 virus
  - Attenuation: host-range restriction
  - Study CP-178: 1-3 mo and 5-24mo seroneg in NA, SA, EU, AU, Africa (N=720)

- **Δ-M2-2**: live attenuated intranasal vaccine
  - Construct: Deletion of 72AA from c-terminus of M2-2 gene
  - Attenuation: Decreases replication while increasing transcription
  - Evaluated at NIH via CRADA – adults, seropositive children & seronegative children complete. Studies ongoing outside CRADA
MEDI-559 CP-147 Live attenuated RSV vaccine

- Design: Randomized double-blind placebo controlled 1:1
- Population: Seronegative 5-24 mo (N=120)
- Schedule: 3 doses of $10^5$ FFU administered 56 day intervals
- Followed for one year after vaccination (including one full RSV season)

- Vaccine Shedding
  - 56% primarily after Dose 1 indicating induction of functional immune response
- Phenotypic Stability
  - 40% of evaluable samples had partial phenotypic reversion to $tsi$
- Immunogenicity: 95% of vaccinees had 4-fold response to at least one assay
  - 59% microneutralization, 85% anti-F IgG, 90% anti-F IgA
- Safety
  - Solicited Symptoms and Adverse Events balanced
  - Serious Adverse Events balanced
  - Medically Attended Lower Respiratory Tract Illness
    - < 28 days after dose: Vaccine 6 vs. Placebo 1
    - > 28 days after dose: Vaccine 6 vs. Placebo 6
MEDI-534 CP-178 Live vectored RSV-F subunit vaccine

- **Design:** Randomized double-blind placebo controlled 1:1
  - $10^5$ (N=160) and $10^6$ (N=160) in seronegative 5-24 mo
  - $10^4$ (N=80), $10^5$ (N=160) and $10^6$ (N=160) in unscreened 1-3 mo infants

- **Schedule:** 3 doses administered 56 day intervals
- **Followed for one year after vaccination (including one full RSV season)**

- **Vaccine Shedding**
  - 60-70% mostly after Dose1 indicating induction of functional immune response

- **Immunogenicity as measured by 4-fold sero-response**
  - PIV3 HAI: 67-87% in 5-24 mo AND 17-35% in 1-3 mo
  - RSV microneutralization: 30-36% in 5-24 mo AND 0-16% in 1-3 mo

- **Safety**
  - Solicited Symptoms and Adverse Events balanced
  - Serious Adverse Events: excess number of subjects in both $10^6$ cohorts
    - 5 vaccine vs 1 placebo in 5-24 mo
    - 9 vaccine vs 3 placebo in 1-3 mo
  - Medically Attended Lower Respiratory Tract Illness: balanced except in both $10^6$ cohorts for >28 days after dosing (within 28 days of dosing balanced)
    - 18 vaccinees vs 10 placebo in 5-24 mo
    - 23 vaccinees vs 15 placebo in 1-3 mo

Dubovsky et al  Presented at IRSVS Nov 2014
Diagnosis-based case definition of lower respiratory tract illness

Motavizumab
- MI-CP117 (N=2,127)
- MI-CP110 (N=6,635)

LRI Definition (+ virologic confirmation)
- Medical diagnosis of pneumonia
- Medical diagnosis of bronchiolitis
- Medical confirmation of cough, retractions, rhonchi, wheezing, crackles, rales
  PLUS
coryza, fever, apnea

RSV infant intranasal vaccines
- MI-CP147 (N=120)
- MI-CP178 (N=780)

LRI Definition (+ virologic confirmation)
- Medical diagnosis of wheezing
- Medical diagnosis of pneumonia
- Medical diagnosis of croup
- Medical confirmation of rhonchi
- Medical confirmation of rales
- Medical diagnosis of bronchitis
- Medical diagnosis of bronchiolitis
- Medical diagnosis of apnea
### Protocol defined LRI terms in infant vaccines studies

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Wheezing</td>
<td>Sustained high pitched, musical breath sounds, during the expiratory phase, which do not clear with cough and must be confirmed by auscultation with stethoscope; must not be transmitted upper airway sounds or inspiratory in nature</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>Persistent rales and crackles originating in the lower respiratory tract, usually accompanied by tachypnea, which do not clear with cough; may be confirmed by x-ray showing areas of consolidation</td>
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<tr>
<td>Croup</td>
<td>Barking cough, hoarseness, and inspiratory stridor (high-pitched whistling sound)</td>
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<tr>
<td>Rhonchi</td>
<td>Persistent coarse breath sounds from the lung or large airways that are not transmitted noises from the upper airway and do not clear with cough or suctioning</td>
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<tr>
<td>Rales</td>
<td>Abnormal lower respiratory tract (ie, lung) sound heard through a stethoscope; may be sibilant (whistling), dry (crackling), or wet, depending on the amount and density of fluid refluxing back and forth in the air passages; does not clear with cough or suctioning</td>
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<tr>
<td>Bronchitis</td>
<td>Coarse large airway rhonchi associated with productive cough; may be accompanied by other signs of respiratory infection or may be allergic</td>
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<tr>
<td>Bronchiolitis</td>
<td>Expiratory wheezing usually associated with signs and symptoms of upper respiratory tract infection, may be confirmed by x-ray showing interstitial infiltrates and hyperinflation</td>
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<tr>
<td>Apnea</td>
<td>Defined by history (observed by lay person) as reported cessation of breathing for 20 seconds or greater with accompanying cyanosis pallor or collapse; breath-holding spells are excluded</td>
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</tbody>
</table>
Proposed objective based RSV LRI definition requires one criteria from each column

<table>
<thead>
<tr>
<th>Specificity</th>
<th>Sensitivity</th>
<th>Medical Significance</th>
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</thead>
<tbody>
<tr>
<td>RSV Confirmed:</td>
<td>Documented PE findings localizing to lower respiratory track:</td>
<td>Objective measures of clinical severity:</td>
</tr>
<tr>
<td>• Positive RT-PCR</td>
<td>• Rhonchi</td>
<td>• Increased respiratory rate</td>
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<tr>
<td></td>
<td>• Rales</td>
<td>• ≥ 60 for &lt; 2 mo</td>
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<tr>
<td></td>
<td>• Crackles</td>
<td>• ≥ 50 for 2-6 mo</td>
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<tr>
<td></td>
<td>• Wheeze</td>
<td>• ≥ 40 for 6-24 mo</td>
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<tr>
<td></td>
<td></td>
<td>• Hypoxemia</td>
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<td></td>
<td></td>
<td>• O₂ saturation &lt; 95% in room air</td>
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<tr>
<td></td>
<td></td>
<td>• Clinical signs of severe respiratory disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• New onset apnea</td>
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<tr>
<td></td>
<td></td>
<td>• Nasal flaring</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Retractions</td>
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<tr>
<td></td>
<td></td>
<td>• Grunting</td>
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<td></td>
<td></td>
<td>• Acute hypoxic or ventilatory failure requiring assisted ventilation</td>
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<td></td>
<td></td>
<td>• Dehydration due respiratory distress requiring IV hydration</td>
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<tr>
<td></td>
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<td>• Prescription medications (only for children with underlying lung disease)</td>
</tr>
</tbody>
</table>
Overview for MEDI8897 Passive RSV Vaccine

Technology
- High potency mAb derived from human B-cells
- YTE half-life extension technology
- High efficiency fermentation and purification

Potential Advantages
- Once per season dosing
- Fixed IM dose (not weight based)
- Vaccine-like pricing

Clinical endpoint
- Prevention of lower respiratory tract illness attributed to RSV
- Prevention of severe RSV illness

Indicated population
- Term infants entering first RSV season
- Pre-term infants entering first RSV season
- Children with CLD/CHD entering first and second RSV season

Project Status
- Phase 1a adult FTiH dosing complete (N=136)
- Phase 1b/2a in 32-35 week GA preterm infants dosing ongoing (N=90)
MEDI8897 blocks RSV F mediated fusion

- Fully human IgG1 mAb derived from human B-cells
- Targets a unique antigenic site on pre-fusion RSV F (distinct from palivizumab)
MEDI8897 demonstrates enhanced activity *in vitro* and *in vivo*

- MEDI8897 targets a unique antigenic site on pre-fusion RSV F
- MEDI8897 neutralizes all RSV A and B clinical isolates tested

- MEDI8897: 9-fold increase in *in vivo* potency compared to palivizumab
- MEDI8897: EC90 identified as target concentration
Distribution of RSV Peak Month by Geographic Zone, n=96

A. Temperate Northern Hemisphere

B. Tropical Northern Hemisphere

C. Temperate Southern Hemisphere

D. Tropical Southern Hemisphere

Bloom-Fesbach et al. PLOSOne 2013; e54445 1-12
Alternative MEDI8897 dosing strategy

- Deliver MEDI8897 as birth dose in term infants
  - Provides protection through first half-year of life where risk of serious RSV disease is greatest
  - Eliminates need for RSV surveillance to identify timing of seasonal dosing
  - Takes advantage of pre-existing medical contacts eliminating need to establish seasonal vaccination campaigns

- Pursue parallel clinical development as birth-dose in tropical regions with irregular RSV transmission
  - Massive unmet medical need and mortality in developing countries
  - Accelerate availability in developing countries
  - Seek label indication for use as birth-dose
  - Generate relevant safety & efficacy data to facilitate deployment in individual countries
Data Supporting Efficacy of Passive RSV Vaccination in Term Infants and when administered as a Birth Dose

- Passive vaccination with motavizumab effective in term infants\(^1\)
  - Randomized 2:1 Native American term infants to 5 monthly doses (N=2,127)
  - Mean age at dosing approximately 2 months of age (SD± 1.9 months)
  - RSV Hospitalization: 8.3% placebo vs 1.4% motavizumab; 83% relative reduction
  - RSV Outpatient LRI: 9.5% placebo vs 2.8% motavizumab; 71% relative reduction

- Passive vaccination with palivizumab effective as birth doses in tropics\(^2\)
  - Taiwan has a blend of year-round and twice-yearly RSV epidemics
  - 6 monthly doses initiated at hospital discharge irrespective of season (N=127)
  - Compared to historical rates of RSV hospitalization
  - Median age at dosing approximately 3 months (IQR 1-6 mo)
  - RSV Hospitalization within 6 months 86% (95% CI: 36-97)
  - RSV Hospitalization within 12 months 78% (95% CI: 40-92)

1: Chandran et al. Presented at PAS May 4 2008
2: Chi et al PLoS One June 2014
**Indication:** Passive immunization of all infants entering their first RSV season and children with CLD/CHD entering their first and second RSV season for the prevention LRI caused by RSV

**Dose:** Single 0.5ml dose delivered by IM injection at beginning of RSV season; larger dose for children in second season

**Duration:** through temperate climate winter viral season (~ 6mo)

**Stability:** no less than 2 years 2-8°C

**Presentation:** 0.5 ml nominal fill in single dose vial

**Indication:** Passive immunization of all infants in the first year of life for the prevention of (severe) lower respiratory tract illness caused by RSV

**Dose:** Single 0.5ml dose delivered by IM injection as a birth-dose

**Duration:** approximately through the first 6-8 months of life

**Stability:** no less than 2 years 2-8°C

**Presentation:** TBD
MEDI8897: Passive RSV vaccine to address global public health needs

- Validated target and approach to address a high unmet medical need
- Novel use of a monoclonal antibody leveraging technological advances
  - Passive vaccination for general population
  - Once per season dosing
  - Tiered vaccine-like pricing
- Opportunity to execute a parallel developed/developing world strategy to facilitate availability in LICs/LMICs on similar timeline to developed countries