LAIV For Increasing Pandemic Vaccine Supply

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This presentation contains discussion of MedImmune’s proprietary live attenuated influenza virus vaccine

LAIV has been approved by the United States Food and Drug Administration for seasonal influenza since 2003 and is also approved in several other countries globally for use in eligible individuals 2-49 years of age (In the EU, for 2-17 years and in Canada, 2-59 years)

LAIV is not approved in Switzerland
Licensed Influenza Vaccines

**TIV**
Trivalent Inactivated Influenza Vaccine, Intramuscular or Intradermal

HA is the only standardized component; other antigens may be present

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**LAIV**
Live Attenuated Influenza Vaccine, Intranasal

Attenuated vaccine with multiple antigens

Please refer to the specific prescribing information for each manufacturer’s influenza vaccine as not all influenza vaccines are indicated for all ages.

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M1, M2=matrix proteins.

3. Prescribing information. Gaithersburg, MD: MedImmune, LLC.
Manufacturing

Seasonal and 2009 H1N1 Pandemic LAIV
LAIV Production in Eggs

Vaccine Seed → Egg → Allantoic Fluid Harvest → Clarification → Centrifugation → Sterile Filtration → Accuspray (Fill/Finish)
### LAIV Yield in Eggs

<table>
<thead>
<tr>
<th>2011/12 Formulation Strains</th>
<th>Average Potency (Log$_{10}$ FFU/ml)</th>
<th>Formulation Target (Log$_{10}$ FFU/Dose)</th>
<th>Dose Per Egg</th>
</tr>
</thead>
<tbody>
<tr>
<td>A/California/07/2009* H1N1</td>
<td>10.2</td>
<td>7.36</td>
<td>148</td>
</tr>
<tr>
<td>A/Perth/16/2009 H3N2</td>
<td>9.8</td>
<td>7.2</td>
<td>85</td>
</tr>
<tr>
<td>B/Brisbane/60/2008</td>
<td>9.8</td>
<td>7.45</td>
<td>48</td>
</tr>
</tbody>
</table>

**Average Number of Monovalent Doses Per Egg** 94

* A/California/07/2009 was the 2009 Pandemic vaccine strain.
Production of 2009 H1N1 Pandemic LAIV Seed

**Phase 1**
- Cloned Swine Flu HA & NA
- Constructed 6 vaccines
- Preliminary characterization
  - Growth about 10X too low
  - Poor filtration

**Phase 2**
- Modify HA
  - Passage (cells & eggs)
  - Sequence
  - Construct derivatives
  - Better growth, but still too low
  - Better filtration
  - Some variants not antigenically correct

**Phase 3**
- Combine most promising changes
- Characterize & Select
  - Seed: A/CA/09 V5 119E/186D
  - Grows well in eggs
  - Filters well
  - Characteristic traits: ca, ts, att
  - Antigenically accurate
  - Immunogenic in animals

**Timeline**
- April: Received 2 Swine Flu Isolates
- May: Phase 1
- June: Phase 2
- July: Phase 3, Begin Bulk Manufacturing
LAIV was first pandemic vaccine shipped to the US government
- Provided ~25% of US doses
- Significant use by children
LAIV is Adaptable to Cell Culture Production

- Of 13 cell substrates assessed, only MDCK cells had all the requisite characteristics for manufacturing LAIV.
  - MRC-5, WI-38; human diploid cells used for other vaccines
  - 293, CHO, FRhL-2, MDCK, NIH 3T3, Vero and other mammalian continuous cell lines
  - CEF, CEK, DF-1 and other avian cell lines

- A limited number of MDCK cell clones supported higher levels of virus productivity

![Graph showing range of virus titer (log FFU/mL) and number of clones](image)

Productivity stable over 25 passages
Estimated Production Times in Eggs or Cell Culture

- Time from strain ID to seed generation unchanged
- Time to produce bulk vaccine reduced by 2 or more months

![Graph showing cumulative bulk doses (x1,000) over weeks in production for cell production and egg production. Bioreactors and eggs are indicated.]
Plasmid Rescue Eliminates AVA Risks

- LAIV vaccines are 6:2 reassortants
- The internal genes of cell and egg produced vaccines are genetically identical

Plasmid rescue eliminates the risk from any potential contaminants in the wild type (human) isolate
Intranasal Administration of Large Particle Mist
Manufacturing Summary

- Produced in specific pathogen-free eggs
  - High yields per egg
  - Relatively simple production process
  - Relatively complex testing
  - Could be adapted to cell culture production
    > Cell culture could shorten the total production time, but not the time to production of the first doses
    > Reverse genetics engineering of vaccine seed reduces risk of any adventitious agent present in original isolate

- Needle-free administration

- Storage at refrigeration temperatures
  - Shelf life of 18 weeks
Safety, Efficacy and Immunogenicity

Seasonal LAIV
## Summary of Solicited Events in Children

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo-controlled studies 2 to 6 years of age&lt;sup&gt;1-2&lt;/sup&gt;</th>
<th>TIV-controlled study 2 to 6 years of age&lt;sup&gt;3&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LAIV (N=876-1,759) %</td>
<td>LAIV (N=2,170) %</td>
</tr>
<tr>
<td>Runny nose/nasal congestion</td>
<td>58</td>
<td>51</td>
</tr>
<tr>
<td></td>
<td>Placebo (N=424-1,034) %</td>
<td>TIV (N=2,165) %</td>
</tr>
<tr>
<td></td>
<td>50</td>
<td>42</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>21</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>17</td>
<td>12</td>
</tr>
<tr>
<td>Irritability</td>
<td>21</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>19</td>
<td>11</td>
</tr>
<tr>
<td>Decreased activity (laziness)</td>
<td>14</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>11</td>
<td>6</td>
</tr>
<tr>
<td>Sore throat</td>
<td>11</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>6</td>
</tr>
<tr>
<td>Headache</td>
<td>9</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>Muscle aches</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Chills</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Fever*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>100º-101ºF Oral</td>
<td>9</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>101º-102ºF Oral</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>

Data from 2 pooled placebo-controlled studies and 1 TIV-controlled study<sup>4</sup>

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4. Prescribing information. Gaithersburg, MD: MedImmune LLC
In children 6-11 months, hospitalizations through 180 days were increased in LAIV recipients
- 6.1% LAIV vs. 2.6% TIV (P=0.002)

Among children 6-23 months of age, LAIV was associated with increased rates of wheezing through 42 days
- 6-11 months: 6.9% LAIV vs. 4.2% TIV (P=0.03)
- 12-23 months: 5.4% LAIV vs. 3.6% TIV (P=0.03)

Among children 24-59 months, neither wheezing nor hospitalizations were increased among LAIV recipients
- Wheezing: 2.1% LAIV vs. 2.5% TIV
- Hospitalization: 2.1% LAIV vs. 2.5% TIV

Summary of solicited adverse events in healthy adults aged 18 years to 49 years

<table>
<thead>
<tr>
<th>Event</th>
<th>LAIV (n=2,458) %</th>
<th>Placebo (n=1,290) %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Runny nose*</td>
<td>44</td>
<td>27</td>
</tr>
<tr>
<td>Headache*</td>
<td>40</td>
<td>38</td>
</tr>
<tr>
<td>Sore throat*</td>
<td>28</td>
<td>17</td>
</tr>
<tr>
<td>Tiredness/weakness</td>
<td>26</td>
<td>22</td>
</tr>
<tr>
<td>Muscle aches</td>
<td>17</td>
<td>15</td>
</tr>
<tr>
<td>Cough</td>
<td>14</td>
<td>11</td>
</tr>
<tr>
<td>Chills</td>
<td>9</td>
<td>6</td>
</tr>
</tbody>
</table>

Summary of solicited events reported within 7 days of either vaccine or placebo (normal egg allantoic fluid) administration in healthy adults 18 years to 49 years of age.

21 studies support the safety and tolerability of LAIV in adults:

- Solicited events and adverse events were mostly mild and transient upper respiratory and systemic symptoms
- SAE rates were low (≤1.5% in the largest studies) and balanced between treatment groups
Meta-Analysis of LAIV Pediatric Efficacy Studies

- 9 randomized, controlled trials between 1997 and 2005
  - 6 placebo-controlled
  - 3 TIV-controlled

- Mostly healthy children previously unvaccinated against influenza
  - 25,000 children aged 6 to 71 months
  - 2,000 children aged 6 to 17 years with asthma

- Primary endpoint: rates of culture-confirmed influenza illness associated with vaccine-similar strains

High Efficacy Relative to Placebo
6 Randomized Studies; Matched Strains
14,000 Children 6–71 Months of Age

- 60% reduction (95% CI: 51, 68)
- 77% reduction (95% CI: 72, 80)
- 87% reduction (95% CI: 81, 90)

Incidence of Influenza (Matched Strains)

- One dose in first season (previously unvaccinated)
- Two doses in first season (previously unvaccinated)
- Revaccination with one dose in second season (previously vaccinated)

Unvaccinated
LAIV

Higher Efficacy Relative to TIV

3 Randomized Studies
13,000 Children 6 Months to <18 Years of Age

- Children 6 – 59 months of age
  - 249 study sites in 16 countries (40% in USA); 8,475 children randomized 1:1
  - 2004-05 season: Matched H1N1, mismatched H3N2, matched/mismatched B

- Children 6 – 71 months of age
  - 114 study sites in 9 EU countries; 2,187 children randomized 1:1
  - 2002 – 03 season: Matched H1N1 and B strains, matched/mismatched H3N2

- Children 6 – 17 years of age with asthma history
  - 145 study sites in 13 EU countries; 2,229 children randomized 1:1
  - 2002-03 season: Matched H1N1 and B strains, matched/mismatched H3N2

Primary efficacy endpoint in each study was culture-confirmed influenza illness associated with vaccine-similar strains

Higher Efficacy Relative to TIV
3 Randomized Studies; Matched Strains
13,000 Children 6 Months – <18 Years of Age


Incidence of Influenza (Matched Strains)

Age

6–59 mo

6–71 mo

6–17 y with asthma

44% reduction (95% CI: 22, 61)
53% reduction (95% CI: 22, 72)
35% reduction (95% CI: 4, 56)

TIV
LAIV

1.4%
2.3%
6.4%

2.4%
4.8%
4.1%
LAIV Efficacy Against Mismatched Strains

Two Studies

9,833 Children 6 – 85 Months of Age

86% reduction (95% CI: 75, 92)
79% reduction (95% CI: 71, 86)
6% reduction (95% CI: –32, 33)

Incidence of Culture-Confirmed Influenza

Mismatched A/H3N2 (1997–98)
26–85 months

Mismatched A/H3N2 (2004–05)
6–59 months

Mismatched B (2004–05)
6–59 months

Relative Efficacy of LAIV and TIV
Efficacy Against All Strains Regardless of Match
Children and Adults

Ambrose et al., Influenza Other Respi Viruses, 5:67-75, 2011
■ In 2 placebo-controlled studies, efficacy following 2 doses of LAIV was comparable through 9 – 12 months following vaccination.
■ In 2 placebo-controlled studies, efficacy persisted throughout the second season without revaccination.

In 3 TIV-controlled studies, the relative efficacy of LAIV versus TIV for matched strains increased with time in each study:

- 0 to 4-month period: 34% (95% CI: 3, 55)
- >4 to 8-month period: 62% (95% CI: 42, 76)

Results are best explained by a decline in TIV efficacy over time.

Seroconversion and Efficacy
All Children Regardless of Baseline Serostatus
Matched Strains

A/H1N1 responses
- Belshe, year 1
- Belshe, year 2
- Tam, year 1
- Tam, year 2
- Vesikari, year 1
- Vesikari, year 2
- Bracco, year 1
- Bracco, year 2

A/H3N2 responses
- Belshe, year 2
- Tam, year 1
- Tam, year 2
- Vesikari, year 1
- Vesikari, year 2
- Bracco, year 1
- Bracco, year 2

B responses

<table>
<thead>
<tr>
<th></th>
<th>Seroresponse (HAI), %</th>
<th>Efficacy (matched strains), %</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A/H1N1</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Belshe, year 1</td>
<td>48/60</td>
<td>81/100</td>
</tr>
<tr>
<td>Belshe, year 2</td>
<td>41/60</td>
<td>81/100</td>
</tr>
<tr>
<td>Tam, year 1</td>
<td>60/81</td>
<td>100/160</td>
</tr>
<tr>
<td>Tam, year 2</td>
<td>28/100</td>
<td>100/160</td>
</tr>
<tr>
<td>Vesikari, year 1</td>
<td>47/92</td>
<td>100/160</td>
</tr>
<tr>
<td>Vesikari, year 2</td>
<td>50/90</td>
<td>100/160</td>
</tr>
<tr>
<td>Bracco, year 1</td>
<td>56/94</td>
<td>100/160</td>
</tr>
<tr>
<td>Bracco, year 2</td>
<td>28/94</td>
<td>100/160</td>
</tr>
</tbody>
</table>

| **A/H3N2**     |                       |                               |
| Belshe, year 2 | 5/100                 | 100/160                       |
| Tam, year 1    | 32/86                 | 100/160                       |
| Tam, year 2    | 32/86                 | 100/160                       |
| Vesikari, year 1 | 25/90               | 100/160                       |
| Vesikari, year 2 | 25/90                | 100/160                       |
| Bracco, year 1 | 14/49                 | 100/160                       |
| Bracco, year 2 | 14/49                 | 100/160                       |

| **B**         |                       |                               |
| Did not circulate | 68/91             | 191/254                      |
| Did not circulate | 30/44              | 162/238                      |
| Did not circulate | 26/79              | 182/260                      |
| Did not circulate | 38/82              | 169/258                      |

Bandell et al., *Exp Rev Vaccines*, 2011, *In Press*
LAIV Utilization by American Pediatric Providers

- Use has increased significantly; ~90% of pediatricians stock LAIV
- LAIV use varies among providers; lower with family practitioners

Toback et al., Vaccine, 29:4225-4229, 2011; Toback et al., Annual Conference on Vaccine Research, April 2011
Thank You!