**Prime-boost approaches to influenza vaccination**

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Prime-boost vaccination regimens

- Employ single or multiple vaccine platforms.
- Potential advantages include:
  - potentiation of immune response
  - increased breadth of immune response
  - antigen sparing
  - flexibility in vaccination schedules

Prime-boost: clinical experience with influenza vaccines

- Majority of studies are with H5N1 vaccines.
- Variety of platforms and intervals evaluated.
- Prime-boost regimens resulted in an increase in magnitude and breadth of antibody response.
- Mechanism of priming is largely poorly understood.

Prime-boost: clinical experience with inactivated H5N1 vaccines

<table>
<thead>
<tr>
<th>Priming vaccine</th>
<th>Booster vaccine</th>
<th>Interval</th>
<th>Cross-clade Ab response detected?</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>H5N1 i.v. x MT59</td>
<td>H5N1 i.v. x MT59</td>
<td>16 months</td>
<td>✓</td>
<td>Nicholson et al. 2001; Stephenson et al. 2009</td>
</tr>
<tr>
<td>H5N1 i.v. x MT59</td>
<td>H5N1 i.v.</td>
<td>7 years</td>
<td>✓</td>
<td>Galli et al. 2009</td>
</tr>
<tr>
<td>H5N1 i.v.</td>
<td>Homologous or heterologous clade i.v</td>
<td>1 month or 6 months ✓ (with heterologous clade booster)</td>
<td>Zangwili et al. 2006; Belshe et al. 2011</td>
<td></td>
</tr>
<tr>
<td>H5N1 WV (egg-derived) + alum</td>
<td>Homologous clade WV</td>
<td>12 months</td>
<td>Not tested</td>
<td>Lin et al. 2009</td>
</tr>
<tr>
<td>H5N1 WV ( vero cell-derived) + alum</td>
<td>Heterologous clade WV</td>
<td>12-17 months</td>
<td>✓</td>
<td>Eielch et al. 2009</td>
</tr>
</tbody>
</table>
Prime-boost: clinical experience with H5N1 vaccines using a combination of platforms

<table>
<thead>
<tr>
<th>Priming vaccine</th>
<th>Booster vaccine</th>
<th>Interval</th>
<th>Cross-clade Ab response detected?</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>rHA</td>
<td>ISV</td>
<td>6 years</td>
<td>✓</td>
<td>Treanor et al. 2001; Geij et al. 2008</td>
</tr>
<tr>
<td>DNA</td>
<td>ISV</td>
<td>4 or 24 weeks</td>
<td>✓</td>
<td>Ledgerwood et al. 2011</td>
</tr>
<tr>
<td>DNA</td>
<td>ISV</td>
<td>4, 12, 16 or 24 weeks</td>
<td>✓</td>
<td>Ledgerwood et al. 2013</td>
</tr>
<tr>
<td>Ad5 vectored vaccine x 3</td>
<td>ISV</td>
<td>3.5-15 months</td>
<td>✓</td>
<td>Gurwith et al. 2013</td>
</tr>
</tbody>
</table>

Priming by pandemic AA ca live attenuated influenza vaccines (pLAIV)

- H5N1 and H7 AA ca pLAIV were highly restricted in replication in healthy seronegative adults.
- H5N1 and H7 pLAIV elicited variable HAI, MN and ELISA Ab responses: H7N3 ca > H5N1 ca > H7N7 ca.
- Previous recipients of H5N1 and H7 pLAIV were recalled to receive a single dose of inactivated subvirion vaccine (ISV) of the corresponding subtype.

H5N1 pLAIV-ISV sequential vaccination study (JHU)

<table>
<thead>
<tr>
<th>Group</th>
<th>Previous pLAIV vaccination</th>
<th>Number of doses ISV</th>
<th>Time interval between prime and boost</th>
<th>Number of subjects enrolled</th>
<th>Number of SAEs</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H5N1 VN04 ca x 2</td>
<td>1</td>
<td>56 mo</td>
<td>11</td>
<td>1*</td>
</tr>
<tr>
<td>2</td>
<td>H5N1 HK03 ca x 2</td>
<td>1</td>
<td>54 mo</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>H7N3 BC04 ca x 2</td>
<td>1</td>
<td>52 mo</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>No previous LAIV of any kind</td>
<td>1</td>
<td>N/A</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>2</td>
<td>1 mo</td>
<td>20</td>
<td>0</td>
</tr>
</tbody>
</table>

Increased frequency and higher HAI titers in recipients of H5N1 pLAIV

<table>
<thead>
<tr>
<th>Prime</th>
<th>Boost</th>
<th>Frequency of responders and HAI Ab titers on d 28</th>
<th>Frequency of responders and HAI Ab titers on d 56</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>n  %     Range            GMT* %     Range            GMT*</td>
<td></td>
</tr>
<tr>
<td>VN04 ca</td>
<td>11</td>
<td>73      5-1280     222     82     5-960     112</td>
<td></td>
</tr>
<tr>
<td>HK03 ca</td>
<td>10</td>
<td>50      5-480     146     40     5-480     120</td>
<td></td>
</tr>
<tr>
<td>H7N3 ca</td>
<td>7</td>
<td>14      5-160     160     0      NA       NA</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>20</td>
<td>10      5-640     277     10     5-240     120</td>
<td></td>
</tr>
<tr>
<td>VN04 ISV</td>
<td>20</td>
<td>40      5-640     81      50     5-320     76</td>
<td></td>
</tr>
</tbody>
</table>

*GMT in responders.
*HAI assay performed with wt A/VN/1203/04 (H5N1).

Breadth of the neutralizing antibody response in H5N1 pLAIV-primed individuals

pLAIV–ISV studies: Summary and Implications

- Prior receipt of pLAIV primes for
  - Higher titer response to a suboptimal dose of inactivated subunit vaccine
  - Increased frequency of response
  - Rapid response – as early as day 7
  - Greater breadth of reactivity against different clades of H5 viruses, and H7 viruses from North American and Eurasian lineages.

- Implications:
  - Clear evidence of an immune response to pLAIV.
  - Administration of a dose of inactivated vaccine is a useful means of unmasking the immune response to pLAIV.

Limitations of prime-boost studies

- Small numbers of subjects.

- Several studies rely on convenience samples – trials not initially designed to evaluate prime-boost regimen.

- Mechanism not studied.

Recommendations for future studies

- Conduct larger studies.

- Systematic evaluation of regimens using combinations of established and novel vaccine platforms.
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