BVDV2 Field Isolates and Their Genetic Relationships to the BVDV2 in US Cattle Vaccines
BVDV Diversity

• Long been known that BVDV strains differ both genetically and antigenically
• Sequencing of different regions of BVDV genomes shows significant differences
  • Divided into subgenotype (1a-1u, 2a-2c)
• Cross-neutralization studies using antiserum and neutralizations using mAbs showed considerable antigenic variation

Note. Mabs listed on left. BVDV isolates listed across top. A dark square (■) indicates binding.
BVDV Sequencing

• Undertaking study comparing BVDV genetic diversity with antigenic differences
• Sequencing viruses that show genetic differences using 5’ UTR sequences
• Full genome sequencing
• Generate monospecific antisera against a selection of viruses across each subgenotype’s genetic spectrum
• Preparing antisera against 1a, 1b and 2 viruses
• Compare increasing genetic distance to neutralization titers
Vaccine Virus aa Differences
296c/5912c – 3
296c/125c – 16
5912c/125c - 15
BVDV2 E2 protein
Monospecific Antisera

- Chose BVDV2 strains based on phylogenetic analysis – across genetic spectrum
- Infected 2 calves with each virus by intranasal instillation followed at ~day 28 with subcutaneous injection of virus for boost
- Bled out at ~54 days post infection
- Determined Ab titer against homologous virus
Virus neutralization titers for genetically diverse BVDV2 strains as determined using antiserum raised against BVDV2a 296c

<table>
<thead>
<tr>
<th>BVDV2</th>
<th>Neutralization Titer</th>
<th>Log(2) Titer</th>
<th>Log(2) Titer Decrease</th>
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</thead>
<tbody>
<tr>
<td>296c</td>
<td>15287[^1]</td>
<td>13.9</td>
<td>0</td>
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<tr>
<td>53637c</td>
<td>2195</td>
<td>11.1</td>
<td>2.8</td>
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<tr>
<td>1336H</td>
<td>1351</td>
<td>10.4</td>
<td>3.5</td>
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<tr>
<td>5Y</td>
<td>2702</td>
<td>11.4</td>
<td>2.5</td>
</tr>
<tr>
<td>PI12</td>
<td>2521</td>
<td>11.3</td>
<td>2.6</td>
</tr>
<tr>
<td>Parker</td>
<td>4390</td>
<td>12.1</td>
<td>1.8</td>
</tr>
<tr>
<td>AzSpl</td>
<td>1448</td>
<td>10.9</td>
<td>3.0</td>
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<tr>
<td>9231</td>
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<tr>
<td>Victor301</td>
<td>1261</td>
<td>10.3</td>
<td>3.6</td>
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<tr>
<td>Nebraska (1b)</td>
<td>20</td>
<td>4.5</td>
<td>9.4</td>
</tr>
<tr>
<td>C24V (1a)</td>
<td>23</td>
<td>4.3</td>
<td>9.6</td>
</tr>
</tbody>
</table>

[^1]: Reciprocal of the antiserum dilution neutralizing test virus
[^2]: Decrease in neutralization titer from the homologous 296c titer
[^3]: 296c homologous antiserum neutralization titer
BVDV1b E2
Weaknesses revealed in experimental designs

• Genetic distances revealed in these analyses can be significant between isolates of BVDV
  • Includes distances from field and vaccine strains
• Do these distances have an impact in vaccination/challenge studies?
• Many BVDV2 challenge experiments used 890 or 1373 as the virulent challenge – both are near most vaccine viruses genetically
• Many vaccination experiments do not use homologous viruses to determine final vaccination titers
  • Genetic distance of test virus from vaccine virus can have large impact on actual titer
• Phylogenetic analyses often use too few sequences with too few references sequences of too little genetic diversity
BVDV2 E2 protein
Conclusions

• Significant genetic diversity exists in the 5 subgenotypes of BVDV in the U.S.
• Little is known about genetic distances and degree of antigenic diversity
• Antigenic diversity can have a serious impact on how efficacious current MLV vaccines are in protecting against BVDV infections
• Indicates a need to seriously consider genetic relationships between vaccine and challenge viruses