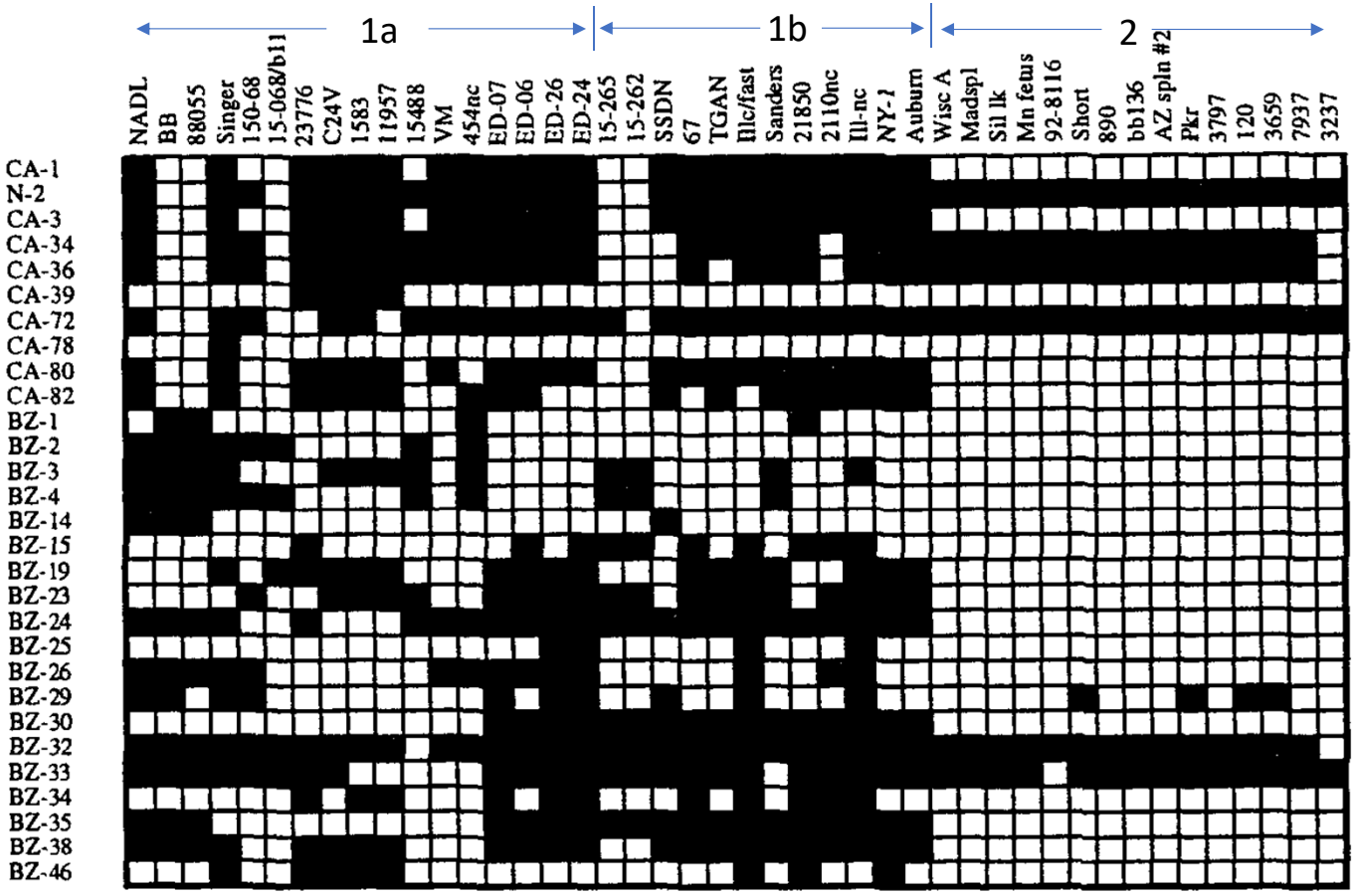
BVDV2 Field Isolates and Their Genetic Relationships to the BVDV2 in US Cattle Vaccines

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.

Ridpath, et al, Virology, 1994

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

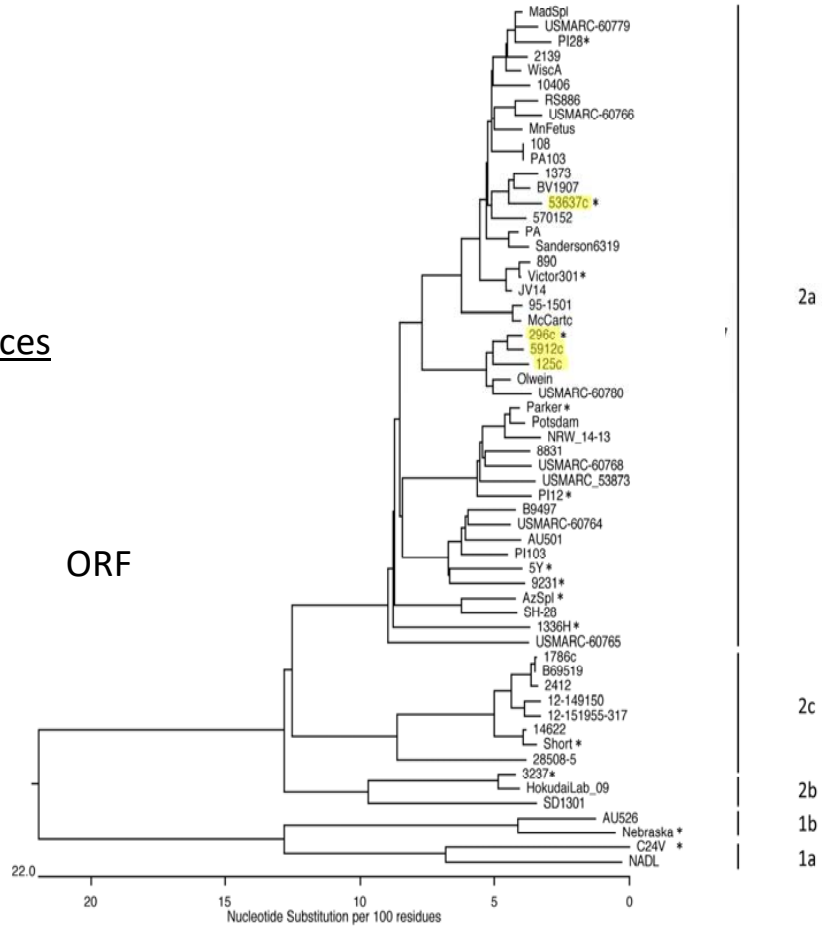
<u>Vaccine Virus aa Differences</u>

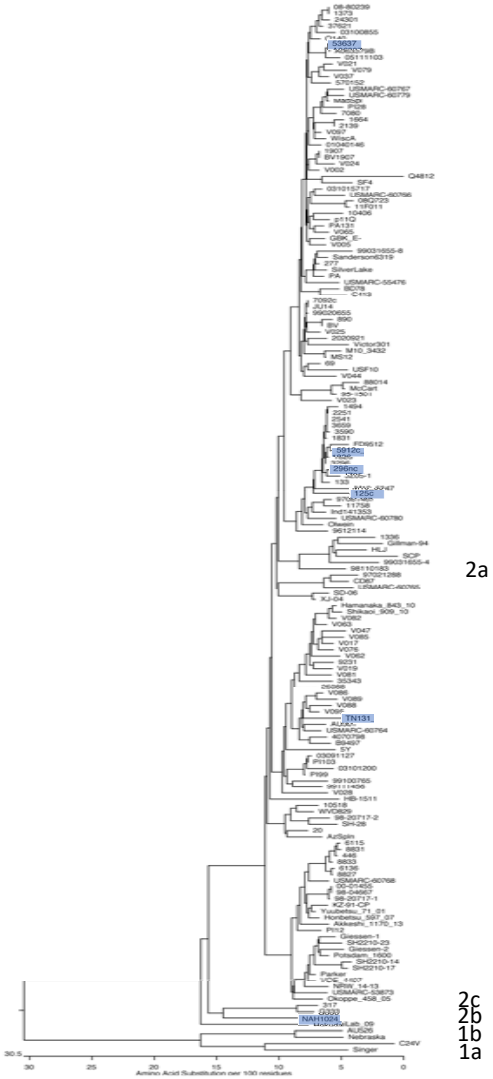
296c/5912c – 3

296c/125c – 16

5912c/125c - 15

ORF





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

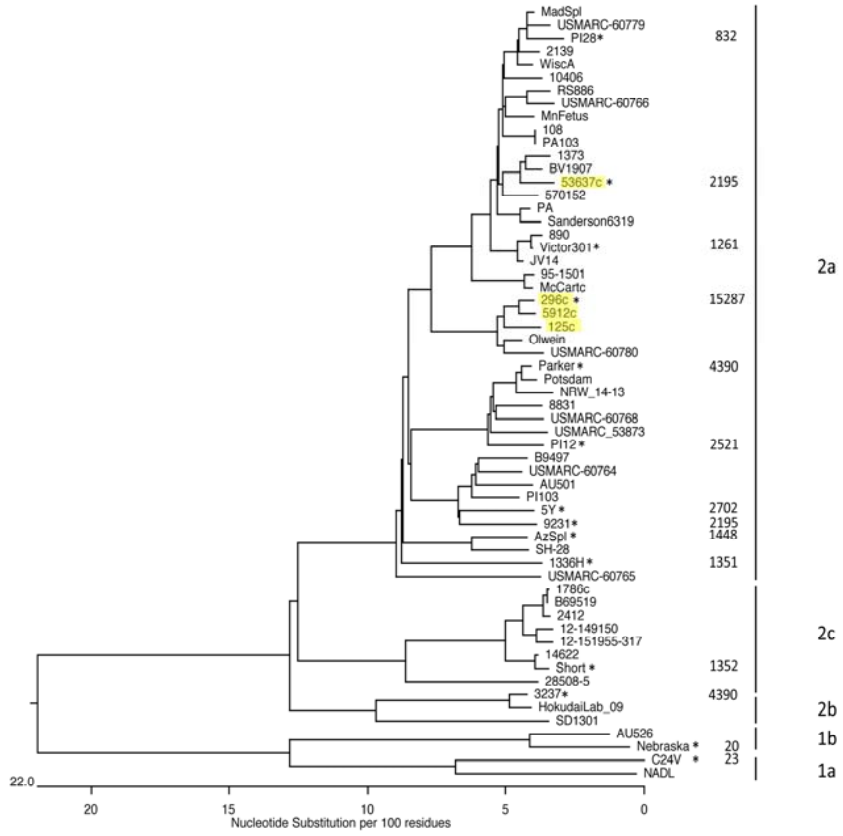
Virus neutralization titers for genetically diverse BVDV2 strains as determined using antiserum raised against BVDV2a 296c

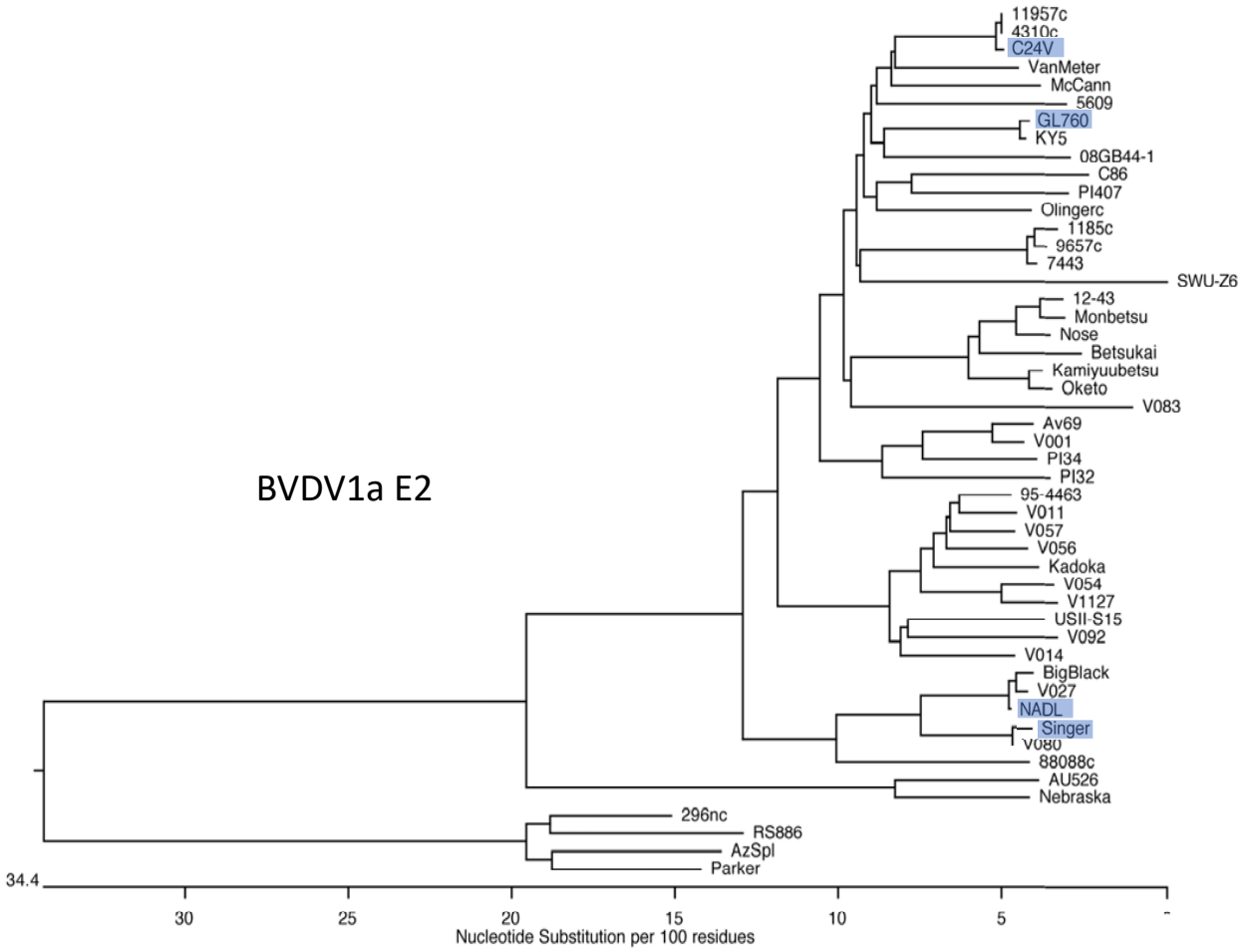
BVDV2	Neutralization Titer[1]	Log(2) Titer	Log(2) Titer Decrease[2]
296c	15287[3]	13.9	0
53637c	2195	11.1	2.8
1336H	1351	10.4	3.5
5Y	2702	11.4	2.5
PI12	2521	11.3	2.6
Parker	4390	12.1	1.8
AzSpl	1448	10.9	3.0
9231	2195	11.1	2.8
Short	1352	10.4	3.5
3237	4390	12.1	1.8
PI28	832	9.7	4.2
Victor301	1261	10.3	3.6
Nebraska (1b)	20	4.5	9.4
C24V (1a)	23	4.3	9.6

[1]Recipricol of the antiserum dilution neutralizing test virus

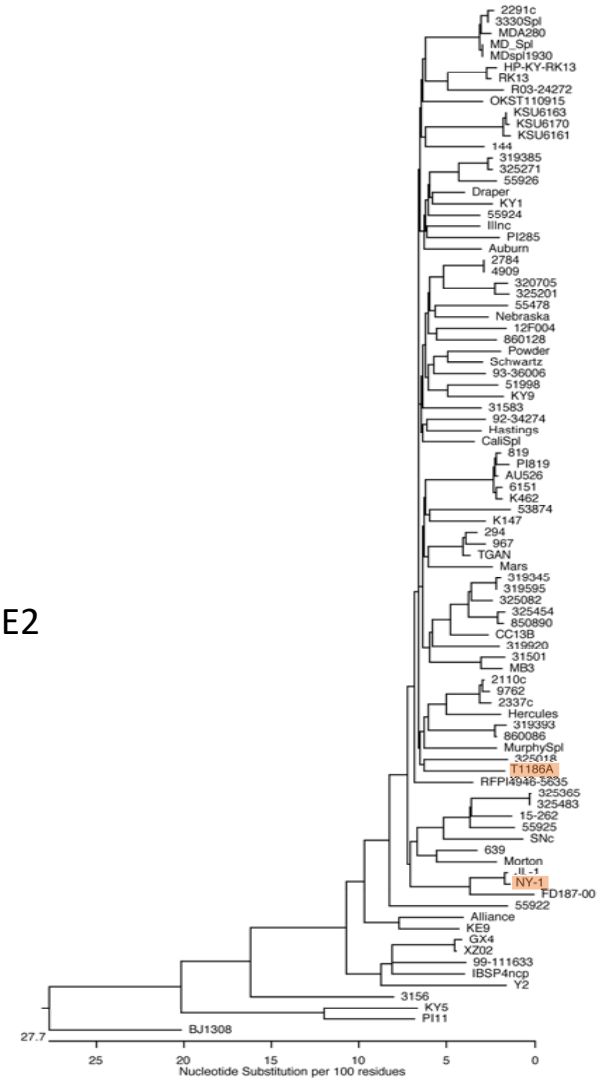
[2]Decrease in neutralization titer from the homologous 296c titer

[3]296c homologous antiserum neutralization titer


MadSpl
USMARC-60779
PI28*
2139
WiscA
10406
RS886
USMARC-60766
MnFetus
108
PA103
1373
BV1907
53637c *
570152
PA
Sanderson6319
890
Victor301*
JV14
95-1501
McCartc
296c *
5912c
125c
Olwein
USMARC-60780
Parker*
Potsdam
NRW_14-13
8831
USMARC-60768
USMARC_53873
PI12*
B9497
USMARC-60764
AU501
PI103
5Y*
9231*
AzSpl *
SH-28
1336H*
USMARC-60765
1786c
B69519
2412
12-149150
12-151955-317
14622
Short*
28508-5
3237*
HokudaiLab_09
SD1301
AU526
Nebraska *
C24V *
NADL
832
2195
1261
15287
4390
2521
2702
2195
1448
1351
1352
4390
20
23
2a
2c
2b
1b
1a
22.0
20
15
10
5
0
Nucleotide Substitution per 100 residues

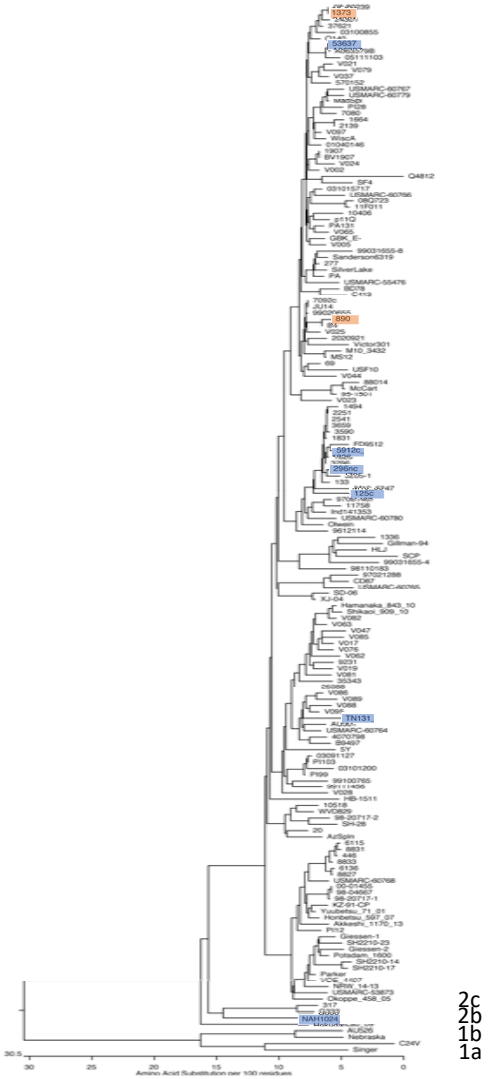

BVDV1a E2
11957c
4310c
C24V
VanMeter
McCann
5609
GL760
KY5
08GB44-1
C86
PI407
Olingerc
1185c
9657c
7443
SWU-Z6
12-43
Monbetsu
Nose
Betsukai
Kamiyuubetsu
Oketo
V083
Av69
V001
PI34
PI32
95-4463
V011
V057
V056
Kadoka
V054
V1127
USII-S15
V092
V014
BigBlack
V027
NADL
Singer
V080
88088c
AU526
Nebraska
296nc
RS886
AzSpl
Parker
1a
1b
2a
34.4
30
25
20
15
10
5
Nucleotide Substitution per 100 residues

BVDV1b E2


2291c
3330Spl
MDA280
MD_Spl
MDspl1930
HP-KY-RK13
RK13
R03-24272
OKST110915
KSU6163
KSU6170
KSU6161
144
319385
325271
55926
Draper
KY1
55924
IIInc
PI285
Auburn
2784
4909
320705
325201
55478
Nebraska
12F004
860128
Powder
Schwartz
93-36006
51998
KY9
31583
92-34274
Hastings
CaliSpl
819
PI819
AU526
6151
K462
53874
K147
294
967
TGAN
Mars
319345
319595
325082
325454
850890
CC13B
319920
31501
MB3
2110c
9762
2337c
Hercules
319393
860086
MurphySpl
325018
T1186A
RFPI4948-5835
325365
325483
15-262
55925
SNc
639
Morton
NY-1
FD187-00
55922
Alliance
KE9
GX4
XZ02
99-111633
IBSP4ncp
Y2
3156
KY5
PI11
BJ1308
27.7
25
20
15
10
5
0
Nucleotide Substitution per 100 residues

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