EpiVax

CircoMatch™: An online tool for prediction of PCV2 vaccine efficacy based on T cell Epitope Content Comparison

zoetis

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Abstract

Background
CircoMatch is an online tool that compares the putative T cell epitope content shared between commercial Porcine Circovirus type 2 (PCV2) vaccines and field isolates to identify which vaccine may confer broader cross-reactive immune response to field isolates based on T cell epitope relatedness.
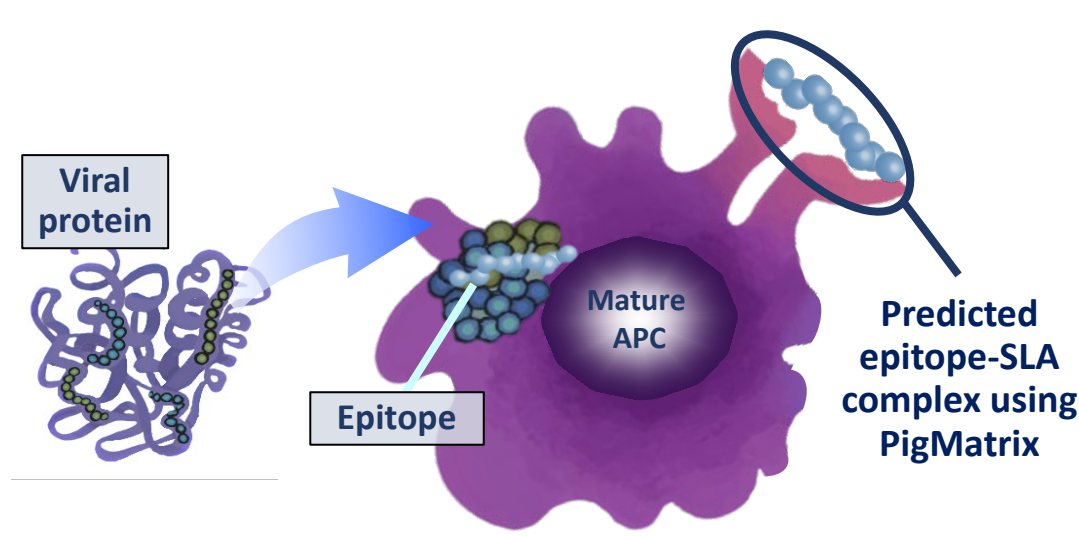
Methods
CircoMatch receives as input one or multiple capsid protein sequences of field isolates and uses PigMatrix to identify putative SLA class I and II T cell epitopes. The Epitope Content Comparison (EpiCC) algorithm assesses the relatedness of T cell epitopes contained in capsid proteins between field isolates and 4 commercial vaccines (3 based on PCV2a, and one a PCV2a and PCV2b bivalent).

Results
CircoMatch generates an EpiCC score for each vaccine-field isolate comparison and a corresponding assessment of T cell epitope coverage. Higher EpiCC scores represent greater relatedness and produce higher T cell epitope coverage. The CircoMatch report includes scales and radar plots for comparison of EpiCC scores calculated for each field isolate-vaccine pair. The EpiCC score scale provides a simple yet effective visual comparison that can be used to rank vaccines for an individual field isolate. The radar plot shows EpiCC scores for each vaccine-field isolate comparison, including reference isolates from different genotypes (PCV2a, b and d), and regions (America, Asia and Europe). EpiCC scores can also be compared to benchmark scores calculated based on comparisons between the vaccines and 746 field isolates from 2017 to 2021.
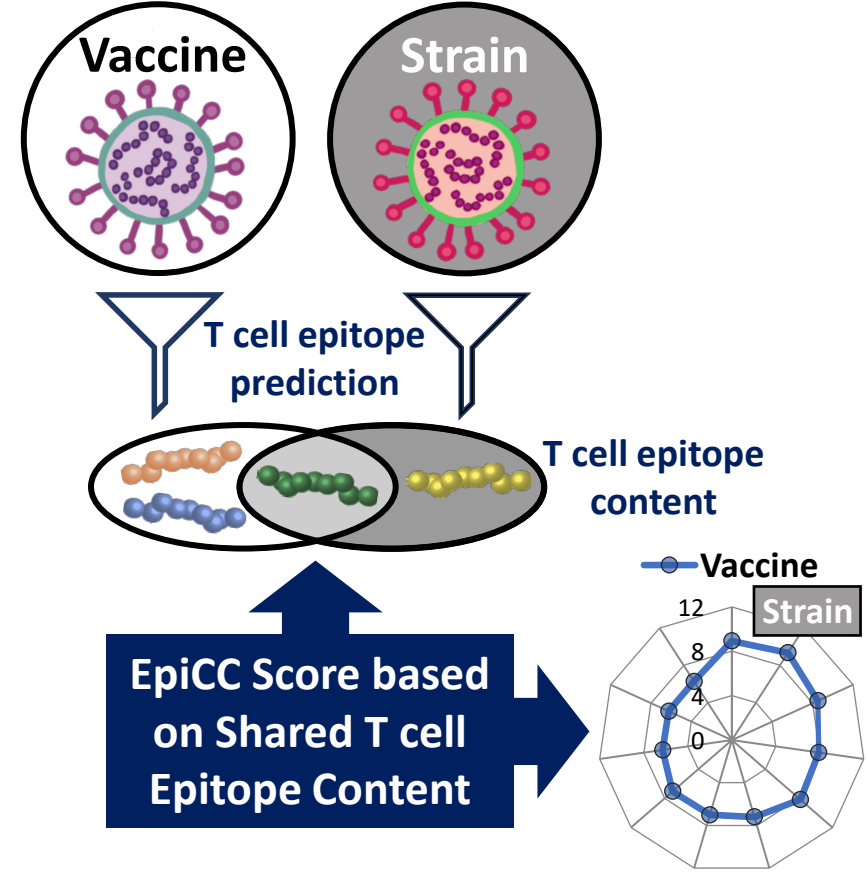
Conclusions
CircoMatch has been developed to help veterinarians and producers select the best-matched commercial vaccine for immunization against circulating PCV2 isolates and to support surveillance to identify variants that may represent a potential threat. Clinical data received as part of the submission may help to refine EpiCC predictions and understand the relationship between shared epitope content and clinical outcomes.

Background

T cell epitope prediction

PigMatrix, built based on the pocket profile method, leverages pocket profiles already constructed for HLA-based epitope prediction in EpiMatrix to predict potential T cell epitopes for SLA class I and II alleles.

T cell Epitope Content Comparison (EpiCC)

Hypothesis: If epitopes in a vaccine closely match the epitopes in a circulating strain, the memory T cells induced by the vaccine are likely to recognize the epitopes in the proteins of the circulating strain.

Application: Analyze existing or proposed vaccines for their potential to protect, based on a comparison between T cell epitopes in the vaccine and circulating strains of the same pathogen.

Methods

INPUT

Submission form

1. Submission information
2. Company information
3. Vaccination information
4. Clinical status
5. Vaccines for comparison
   - 3 Monovalent PCV2a vaccines
   - 1 Bivalent PCV2a-b vaccine (Fostera Gold PCV/CircoMax)
6. Field isolates information
   - Farm name, veterinarian name, sample collection date, sample type, genotype, etc.
7. Capsid protein sequences

IN SILICO ANALYSIS

PigMatrix: CD4 and CD8 T cell epitope prediction

EpiCC: T cell Epitope Content Comparison

EpiCC Score
Strain 1 > Strain 2
Vaccine shares more T cell epitope content with Strain 1.

CIRCOMATCH REPORT

1. Genotypes of PCV2 Isolates Analyzed
2. PCV2 isolates analyzed - Background Information
3. EpiCC Analysis Results

Sequence id	EpiCC Baseline	Vaccines	EpiCC Score	T cell epitope Coverage %
Strain 1	11.084	Vaccine A	9.929	78.54%
		Vaccine B	9.348	74.23%
Strain 2	11.018	Vaccine A	8.654	89.58%
		Vaccine B	8.179	84.34%

4. Phylogenetic Analysis
5. Benchmark EpiCC Scores
6. Field Strain Sequences

EpiCC Score Scale

Comparison of EpiCC scores and ranking of vaccines for individual field isolates or comparison of scores among isolates.

EpiCC Score Radar Plot

Ideal Vaccine: High EpiCC scores, matching the EpiCC Baseline scores of strains.

Vaccine A against all strains: High EpiCC scores, more related T cell epitopes between vaccine and strains.

Vaccine B against all strains: Low EpiCC scores, less related T cell epitopes between vaccine and strains.

Baseline EpiCC: Predicted epitope density of a strain.

CircoMatch™ Report

circo-MATCH

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EpiCC - Epitope Content Comparison for PCV2 Vaccine Suitability
File: ZTS-EpiVax-2022-1
January 1, 2023 (EpiCC Ver 1.1)
Prepared for: ANIMAL VACCINES

1. Genotypes of Porcine Circovirus type 2 (PCV2) Isolates Analyzed

Genotype	PCV2a	PCV2b	PCV2d	Total
Number of sequences	2	2	2	6

2. PCV2 Isolates Analyzed - Background Information

| Sequence id	Submission id	Country	Genotype	Farm Name	Collection date	Veterinarian name	Sample type	PCR Ct values	PCR virus load
1_CAN a	ZTS-EpiVax-2023-1.1	Canada	PCV2a	Farm A	05/15/21	Veterinarian 1	Serum	20.3	2.5 x 10⁸
2_FRA a	ZTS-EpiVax-2023-1.2	France	PCV2a	Farm B	11/03/22	Veterinarian 2	Tissue	24.3	2.8 x 10⁷
3_FRA b	ZTS-EpiVax-2023-1.3	France	PCV2b	Farm B	04/16/21	Veterinarian 2	Tissue	27.1	4.5 x 10¹³
4_FRA b	ZTS-EpiVax-2023-1.4	France	PCV2b	Farm B	10/15/21	Veterinarian 2	Tissue	28.6	1.1 x 10¹¹
5_COL d	ZTS-EpiVax-2023-1.5	Colombia	PCV2d	Farm C	06/29/21	Veterinarian 3	Serum	25.3	2.1 x 10⁵
6_THA d	ZTS-EpiVax-2023-1.6	Thailand	PCV2d	Farm D	12/16/21	Veterinarian 4	Serum	28.1	1.9 x 10⁴

Table sorted by genotype and collection date.

3. EpiCC Analysis Results

Sequence id	Country	Genotype	EpiCC Baseline	Vaccines	Vaccine genotypes	EpiCC Score[1]	T cell epitope Coverage %	Deficit relative to VacAB[2]	VacAB % coverage increase over each monovalent vaccine[3]
1_CAN a	Canada	PCV2a	11.084	VacAB	PCV2a, PCV2b	9.929	89.58%	-	-
				VacAlt1	PCV2a	9.348	84.34%	5.24%	6.22%
				VacAlt2	PCV2a	9.546	86.12%	3.46%	4.01%
				VacAlt3	PCV2a	8.103	73.11%	16.47%	22.53%
2_FRA a	France	PCV2a	11.018	VacAB	PCV2a, PCV2b	8.654	78.54%	-	-
				VacAlt1	PCV2a	8.179	74.23%	4.31%	5.81%
				VacAlt2	PCV2a	8.343	75.72%	2.82%	3.73%
				VacAlt3	PCV2a	7.483	67.92%	10.63%	15.65%
3_FRA b	France	PCV2b	10.867	VacAB	PCV2a, PCV2b	10.722	98.67%	-	-
				VacAlt1	PCV2a	7.243	66.65%	32.01%	48.03%
				VacAlt2	PCV2a	7.688	70.75%	27.92%	39.46%
				VacAlt3	PCV2a	7.946	73.12%	25.55%	34.94%
4_FRA b	France	PCV2b	11.028	VacAB	PCV2a, PCV2b	10.605	96.16%	-	-
				VacAlt1	PCV2a	7.125	64.61%	31.56%	48.84%
				VacAlt2	PCV2a	7.570	68.64%	27.52%	40.09%
				VacAlt3	PCV2a	7.829	70.99%	25.17%	35.46%
5_COL d	Colombia	PCV2d	10.349	VacAB	PCV2a, PCV2b	8.397	81.14%	-	-
				VacAlt1	PCV2a	6.282	60.70%	20.44%	33.67%
				VacAlt2	PCV2a	6.610	63.87%	17.27%	27.03%
				VacAlt3	PCV2a	6.940	67.06%	14.08%	20.99%
6_THA d	Thailand	PCV2d	10.604	VacAB	PCV2a, PCV2b	8.163	76.98%	-	-
				VacAlt1	PCV2a	6.048	57.04%	19.95%	34.97%
				VacAlt2	PCV2a	6.376	60.13%	16.85%	28.03%
				VacAlt3	PCV2a	6.706	63.24%	13.74%	21.73%

[1]Colored according to the EpiCC Score Scale.
[2,3]Metrics of increase in T cell epitope coverage comparing VacAB (bivalent) vs. monovalent vaccines.
[2]VacAB % coverage - Monovalent % coverage. [3](VacAB % coverage - Monovalent % coverage)/Monovalent % coverage
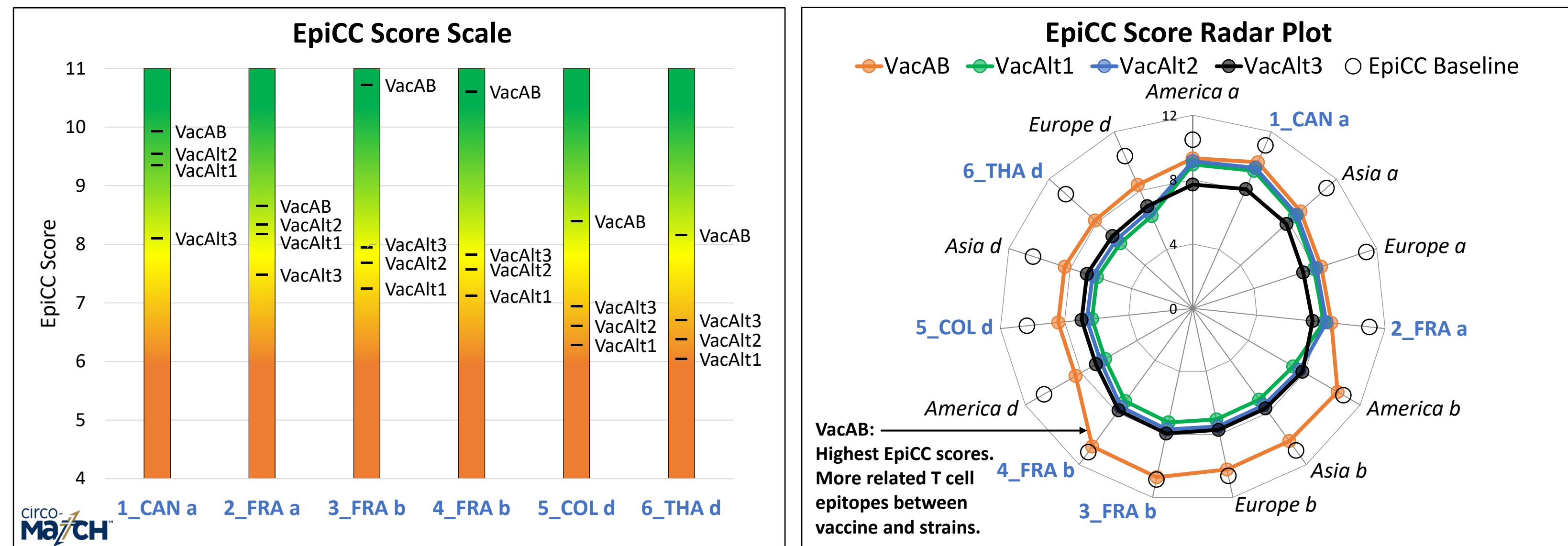
EpiCC Score Scale

The scales show EpiCC Scores for vaccines (y-axis) compared to each field isolate analyzed.

EpiCC Score Radar Plot

VacAB: Highest EpiCC scores. More related T cell epitopes between vaccine and strains.

The radar plot compares EpiCC Scores between vaccines, *representative strains*, and field isolates. Each axis corresponds to the sequence of one strain. Baseline EpiCC Scores for each sequence (open circles) are shown.

INTERPRETATION: VacAB had the highest EpiCC scores for the analyzed PCV2a, PCV2b, and PCV2d isolates. VacAB covers more of the putative T cell epitope content identified in the capsid protein sequence of the PCV2 strains.

4. Phylogenetic Analysis
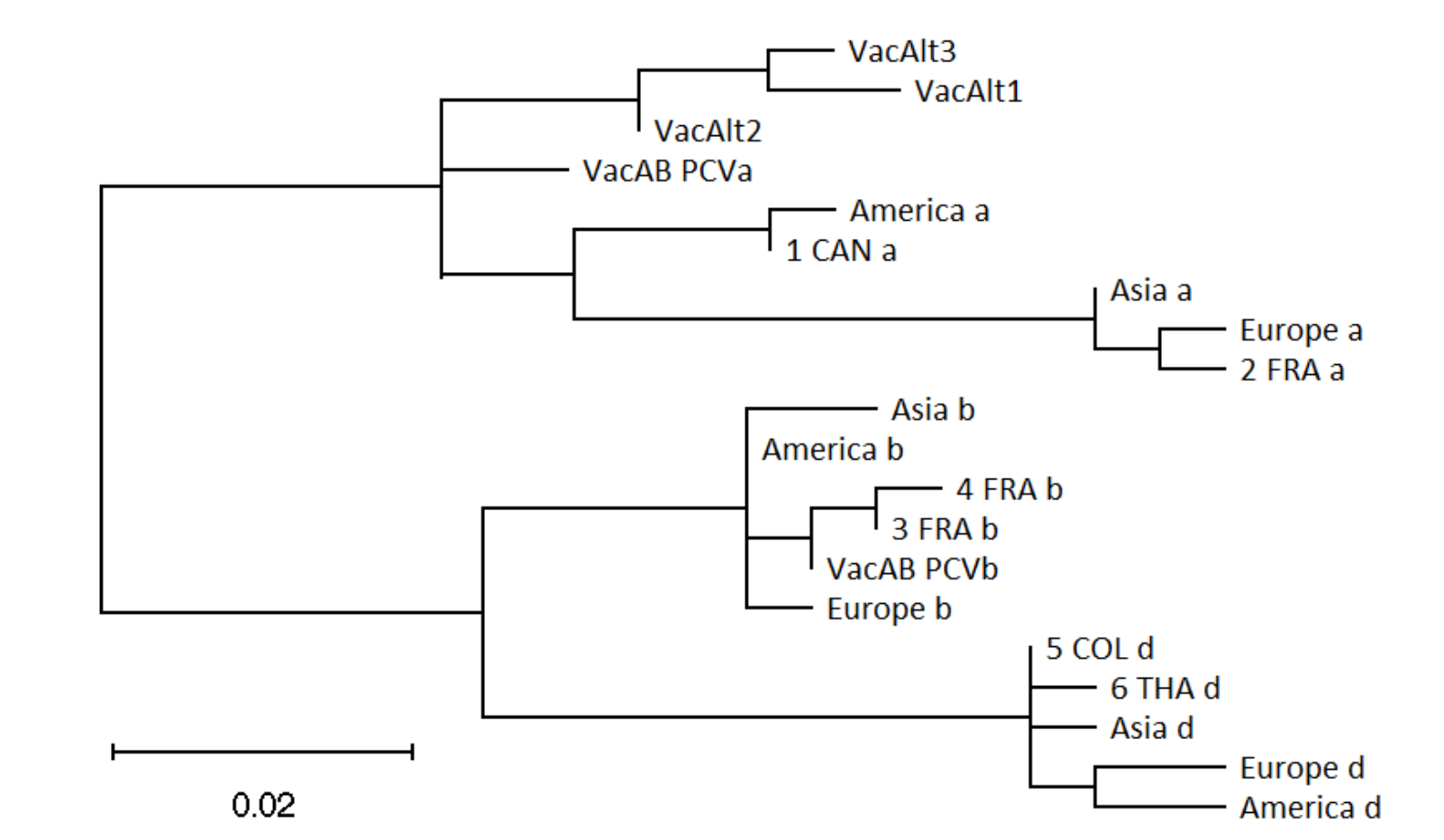
Molecular Phylogenetic analysis by Maximum Likelihood method based on the JTT matrix-based model. The tree with the highest log likelihood (-1159.14) is shown. Initial tree(s) for the heuristic search were obtained automatically by applying Neighbor-Join and BioNJ algorithms to a matrix of pairwise distances estimated using a JTT model, and then selecting the topology with superior log likelihood value.

5. Benchmark EpiCC Scores

For comparison: Benchmark EpiCC scores calculated based on comparisons between vaccines and 746 field isolates.

Vaccine	Field isolate genotype	America N=292; a=82, b=30, d=180 Average (min-max)	Asia N=185; a=13, b=11, d=161 Average (min-max)	Europe N=269; a=34, b=68, d=167 Average (min-max)
VacAB	PCV2a	9.33 (7.80-10.1)	8.96 (8.54-9.93)	8.37 (7.34-8.65)
	PCV2b	10.23 (9.0-10.87)	10.19 (8.9-10.76)	10.23 (9.1-10.87)
	PCV2d	8.37 (7.37-8.74)	8.32 (7.02-8.91)	8.31 (6.34-8.78)
VacAlt1	PCV2a	8.75 (7.13-9.48)	8.51 (7.94-9.71)	7.87 (7.16-8.18)
	PCV2b	6.98 (6.21-7.41)	7.0 (6.06-7.40)	7.06 (5.80-7.48)
	PCV2d	6.26 (5.25-6.63)	6.22 (4.90-6.94)	6.21 (4.37-6.67)
VacAlt2	PCV2a	9.14 (7.38-9.71)	8.82 (8.19-9.66)	8.08 (7.19-8.34)
	PCV2b	7.41 (6.65-7.69)	7.39 (6.50-7.69)	7.38 (6.25-7.76)
	PCV2d	6.58 (5.58-6.95)	6.55 (5.23-7.47)	6.54 (4.73-6.95)
VacAlt3	PCV2a	7.79 (6.43-8.49)	7.65 (7.24-8.46)	7.21 (6.59-7.97)
	PCV2b	7.65 (6.87-7.95)	7.61 (6.76-7.95)	7.64 (6.51-8.22)
	PCV2d	6.92 (5.91-7.56)	6.86 (5.56-7.60)	6.86 (5.03-7.33)

Table is colored according to the EpiCC Score Scale.
References: Foss D, et al. (submitted) and internal Zoetis reports: EpiVaxWO2, EpiVaxWO4, EpiVaxWO5, EpiVaxWO6, EpiVaxWO9, EpiVaxWO10, EpiVaxWO11.

Conclusions

- CircoMatch is an online tool developed to help veterinarians and producers select the best-matched commercial vaccine for immunization against circulating PCV2 isolates and to support surveillance to identify variants that may represent a potential threat.
- In this example, VacAB (bivalent vaccine) had the highest EpiCC scores for the set of analyzed isolates from genotypes PCV2a, PCV2b and PCV2d. This result suggests that VacAB covers more of the putative T cell epitope content predicted in the capsid protein sequences of PCV2 strains.
- Clinical data received as part of the submission may help to refine EpiCC predictions and understand the relationship between shared T cell epitope content and clinical outcomes.
- EpiCC can be applied to evaluate T cell epitope relatedness between swine and human viruses and other circulating strains of pathogens, beyond PCV2.

References

[1] Gutiérrez AH, et al. Development and validation of an epitope prediction tool for swine (PigMatrix) based on the pocket profile method. BMC Bioinformatics. 2015;16,290.

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[3] Gutiérrez, AH, et al. T cell epitope content comparison (EpiCC) of swine H1 influenza A virus hemagglutinin. Influenza Other Respi Viruses.2017;11:531- 542.

[4] Bandrick M, et al. T cell epitope content comparison (EpiCC) analysis demonstrates a bivalent PCV2 vaccine has greater T cell epitope overlap with field strains than monovalent PCV2 vaccines. Vet Immunol Immunopathol. 2020;223:110034.

[5] Bandrick, M, et al. A bivalent porcine circovirus type 2 (PCV2), PCV2a-PCV2b, vaccine offers biologically superior protection compared to monovalent PCV2 vaccines. Vet Res. 2022;53,12.

[6] Foss, D, et al. T cell Epitope Content Comparison (EpiCC) analysis of porcine circovirus type 2 isolates from 2017-2021 confirms the global relevance of a bivalent vaccine approach (under review).