OFFLU SWINE INFLUENZA DATA PACKAGE

JULY 2022 TO DECEMBER 2022

SCOPE

In this document we present a summary of H1 and H3 swine influenza A virus detections.

February 2023

Swine influenza A viruses: Acknowledgements and Methods

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Brief Methods for Genetic and Antigenic Analyses

Analyses were conducted by subtype and lineage or clade. Reference sequences and new data (deposited July 1, 2022 – December 31, 2022) were downloaded from GISAID or GenBank were aligned with MAFFT (Katoh and Standley, 2013) using default settings. Alignments for each segment were inspected manually and trimmed to the start and stop codon. Exploratory trees were run using FastTree (Price et al., 2009). Tabular comparisons between current CVVs or human seasonal vaccine strains and new swine data were generated using the NADC IAV bioinformatic toolkit (https://github.com/flu-crew). A clade representative was selected using PARNAS (https://github.com/flu-crew/parnas) and the best matched available strain was selected for testing against reference ferret antisera in hemagglutination inhibition (HI) assays. All HI assays were performed with ferret anti-sera and guinea pig red blood cells. H3N2 assays were performed with the addition of oseltamivir.

Global influenza A events in swine

Epidemiology

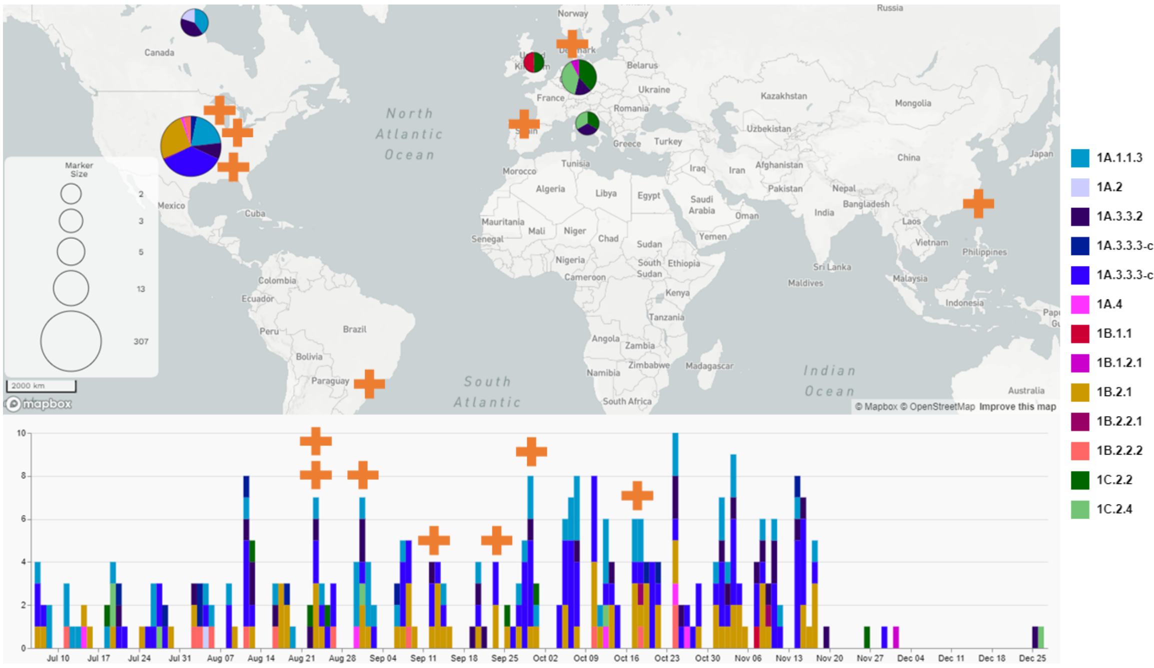


Figure 1. MicroReact map of swine IAV H1 HA genes colored by phylogenetic clade for sequences collected and deposited to GISAID or GenBank between July 1 – December 31, 2022 (n=326); collection date is represented on bottom timeline. Strains submitted with only partial date were assigned a random date to preserve temporal clusters. Geographic nodes scaled to detection proportions. Clades containing variants, location, and date of detection are marked with orange crosses.

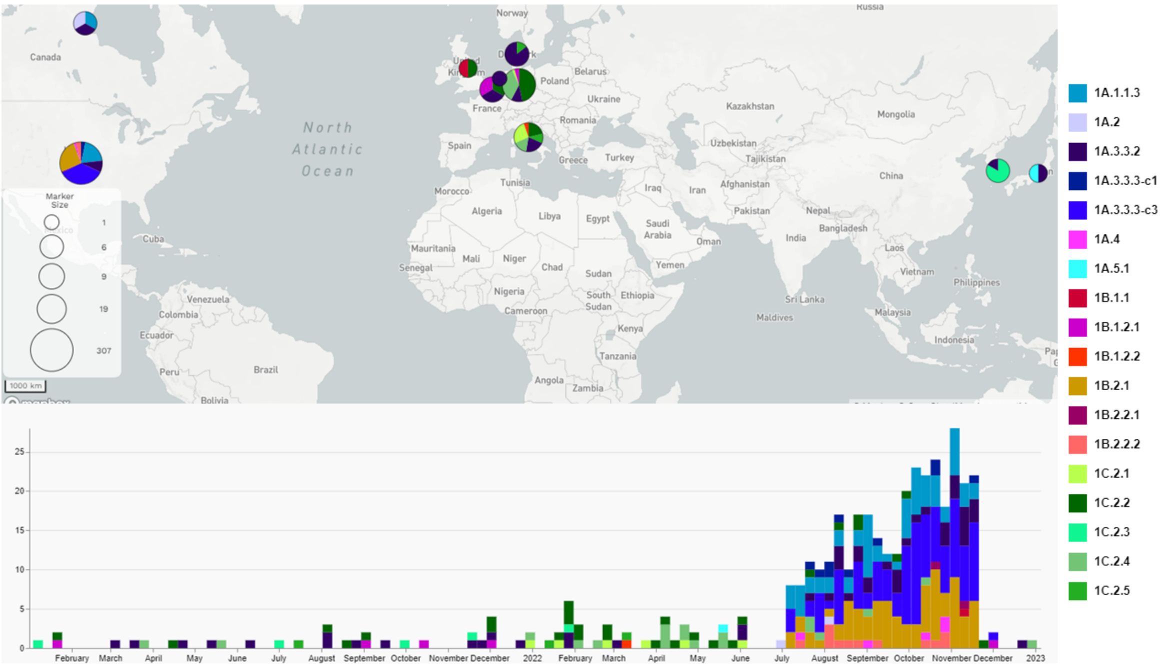


Figure 2. MicroReact map of swine IAV H1 HA genes colored by phylogenetic clade for sequences collected from December 31, 2020 – December 31, 2022 and deposited to GISAID or GenBank between July 1 – December 31, 2022 (n=400); collection date is represented on bottom timeline. Strains submitted with only partial date were assigned a random date to preserve temporal clusters. Geographic nodes scaled to detection proportions.

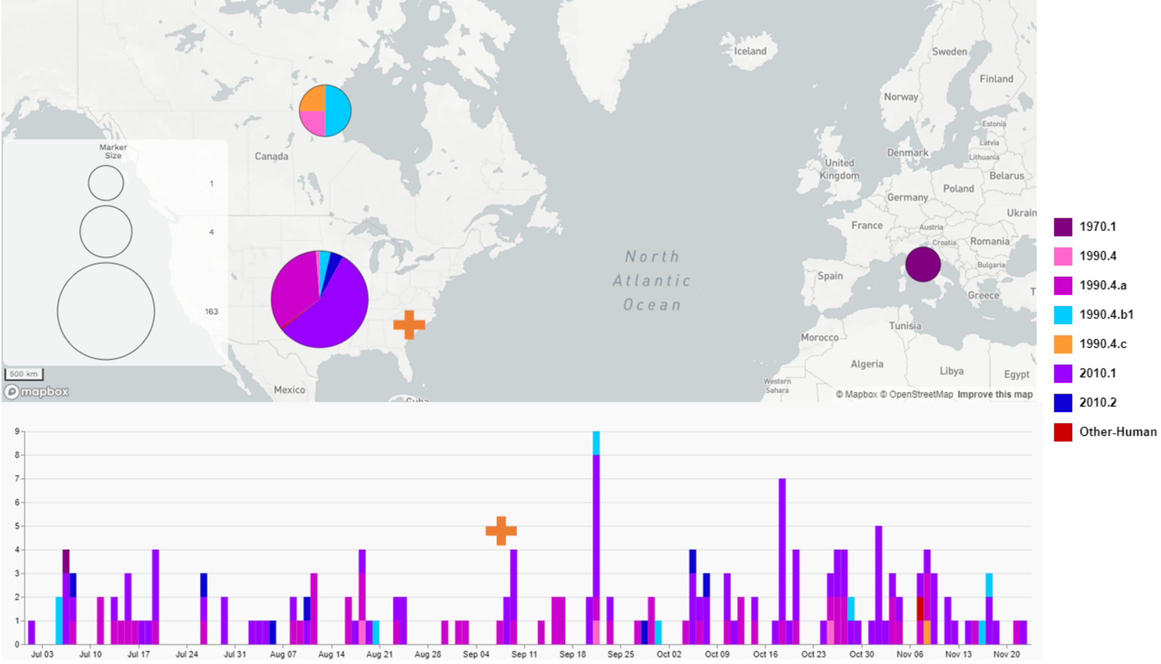


Figure 3. MicroReact map of swine IAV H3 HA genes colored by phylogenetic clade for sequences collected and deposited to GISAID or GenBank between July 1 – December 31, 2022 (n=166). Strains submitted with only partial date were assigned a random date within the provided year to preserve temporal clusters. Geographic nodes scaled to detection proportions. Clades containing variants, location, and date of detection are marked with orange crosses.

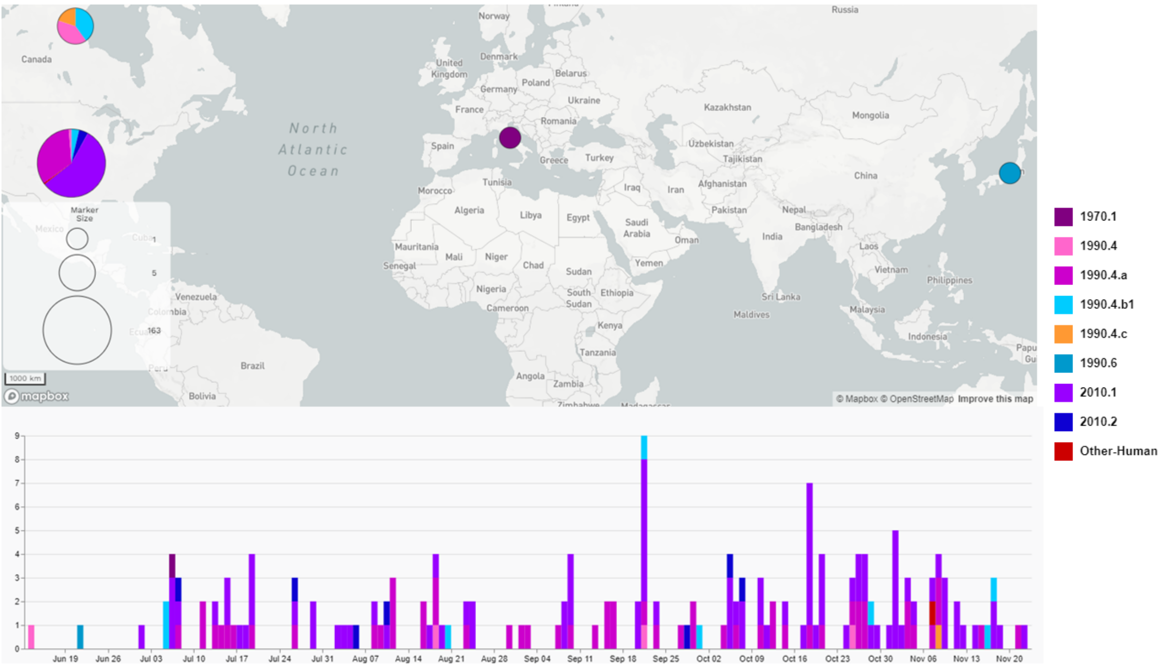
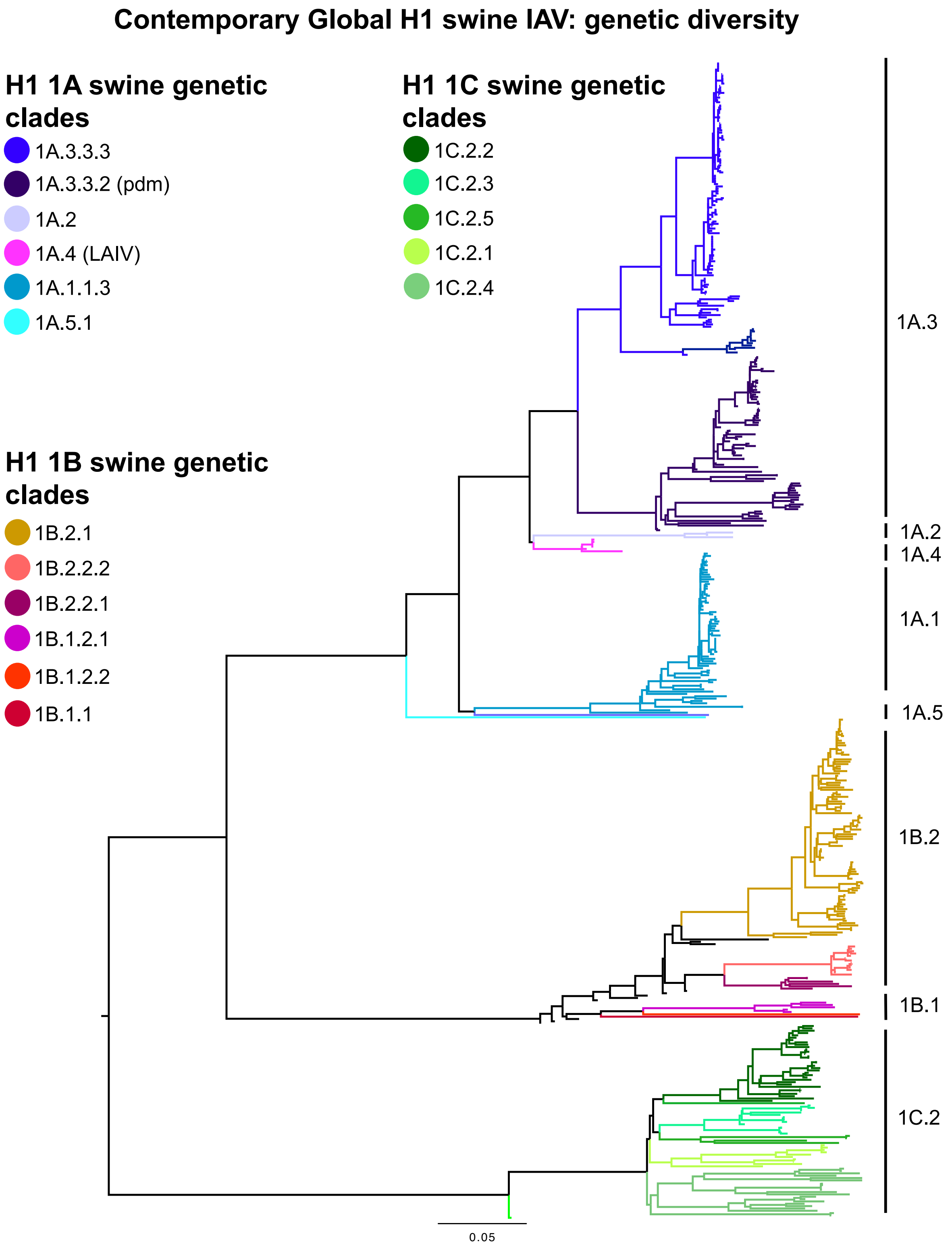
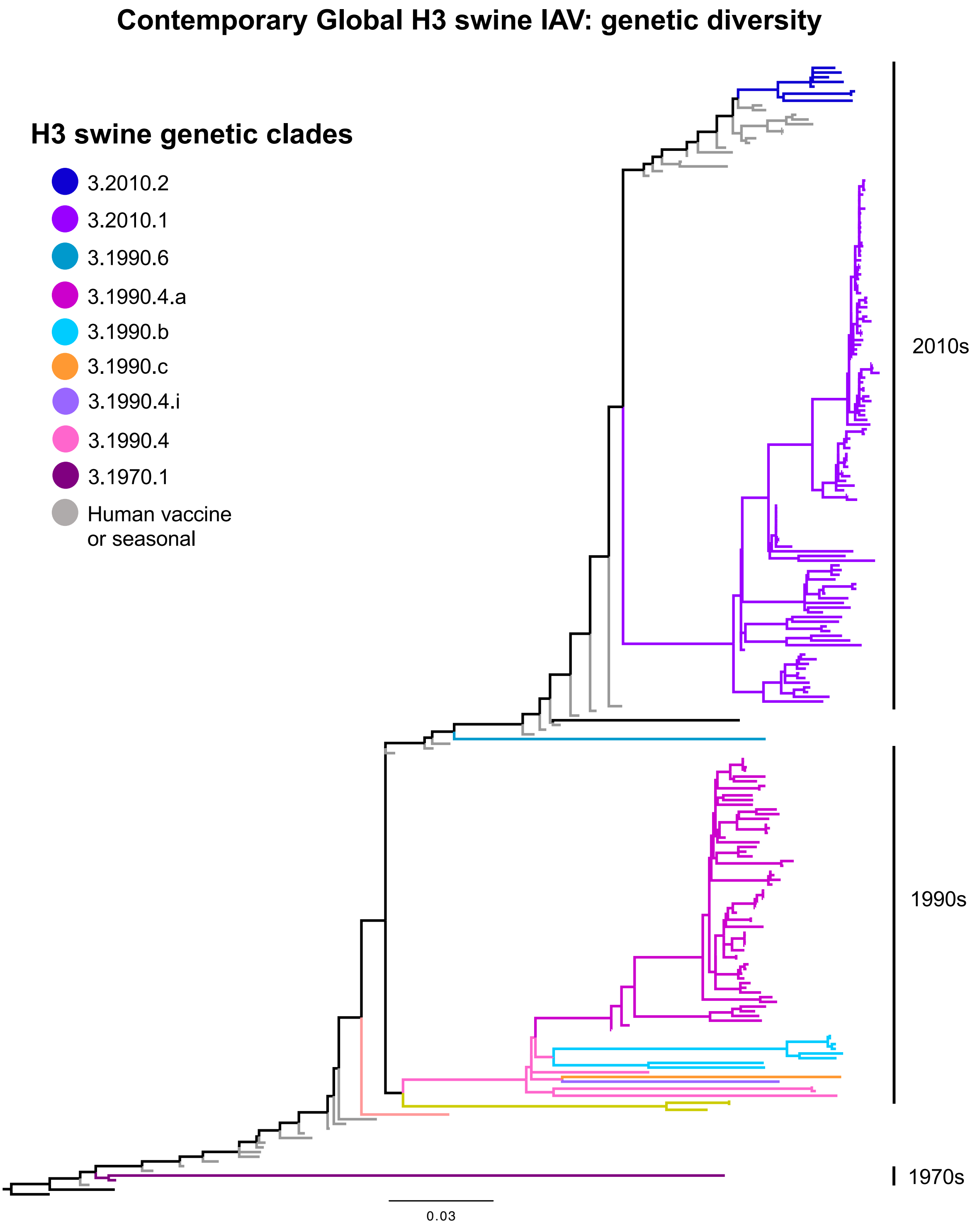


Figure 4. MicroReact map of swine IAV H3 HA genes colored by phylogenetic clade for sequences collected from December 31, 2020 – December 31, 2022 and deposited to GISAID or GenBank between July 1 – December 31, 2022 (n=168). Strains submitted with only partial date were assigned a random date within the provided year to preserve temporal clusters. Geographic nodes scaled to detection proportions.



n=404, data deposited within last 6 months.

Figure 5. Global swine H1 phylogenetic tree colored by clade and annotated by global H1 lineage nomenclature. Analyses were conducted with reference sequences and data (all data deposited July 1, 2022 – December 31, 2022) from GISAID or shared via the OFFLU swine IAV working group.



Contemporary Global H3 swine IAV: genetic diversity

n=170, data deposited within last 6 months, and n=71 reference genes.

Figure 6. Global swine H3 phylogenetic tree colored by clade and annotated by decade of introduction from human seasonal H3. Analyses were conducted with reference sequences and data (all data deposited July 1, 2022 – December 31, 2022) from GISAID or shared via the OFFLU swine IAV working group.

Regional geographic summary

Phylogenetic analysis identified 21 genetic clades from H1 and H3 IAV in swine in sequence data deposited between July 1 - December 31, 2022.

13 clades were H1 subtype, with detections from each of the lineages: 1A classical swine lineage (6 clades); 1B human-seasonal lineage (5 clades); and 1C Eurasian avian lineage (2 clades).

- The 1A classical swine lineage viruses have global detection: 1A.1.1.3 in USA and Canada; 1A.2 in Canada; 1A.4 in USA; 1A.3.3.3-c1 and 1A.3.3.3-c3 in USA. The 1A.1.5.1 were only detected in Japan. The 1A.3.3.2/pdm circulated in all countries that deposited sequence data during this 6-month period (8 countries).
- 1B.1 human seasonal lineage was only in Europe, and the 1B.2 human seasonal lineage was only in the USA.
- The 1C.2 Eurasian avian lineage was detected in Europe. There were 1C detections in South Korea but outside of the July 1 – Dec 31, 2022, period. A first detection of a H1N2v from the 1C.2.5 genetic clade in Taiwan was reported, but there were no available swine surveillance data.
- A novel 1C.2 clade associated with an H1N1v was identified and named 1C.2.6.

8 H3 clades were detected in swine within 4 distinct lineages derived from human seasonal H3 virus spillovers grouped by the decade of introduction (1970.1; 1990.4; 2010.1; 2010.2). The 1990.4 lineage diversified into three co-circulating genetic clades.

- The H3 2010.1 and 2010.2 clades were only detected in the USA, the H3 1970.1 clade was only detected in Europe. The 1990.4 lineage was detected in the USA and Canada.

Global Variant Cases:

During the reporting period (July 1 – December 31, 2022), 14 variant cases were reported and included with the swine analyses:

- **USA: H1N2v (1 1A.1.1.3; 1 1A.3.3.2; 3 1B.2.1;), H3N2v (5 2010.1)**
- **Brazil: H1N1v (1 1A.3.3.2)**
- **Netherlands: H1N2v (1 1C.2.2)***
- **Taiwan: H1N2v (1 1C.2.5)***
- **Spain: H1N1v (1 1C.2.6)***

An additional variant case was detected on April 8 2022, and presented by China CDC that was not described in prior OFFLU reports:

- **China: H1N1v (1 1C.2.3 – no sequence data)**

***Variants are now reported in each named H1 1C.2 clade (1C.2.1 – 1C.2.6); within-clade CVVs are available for 1C.2.1 - 1C.2.4, but not for 1C.2.5 or 1C.2.6.**

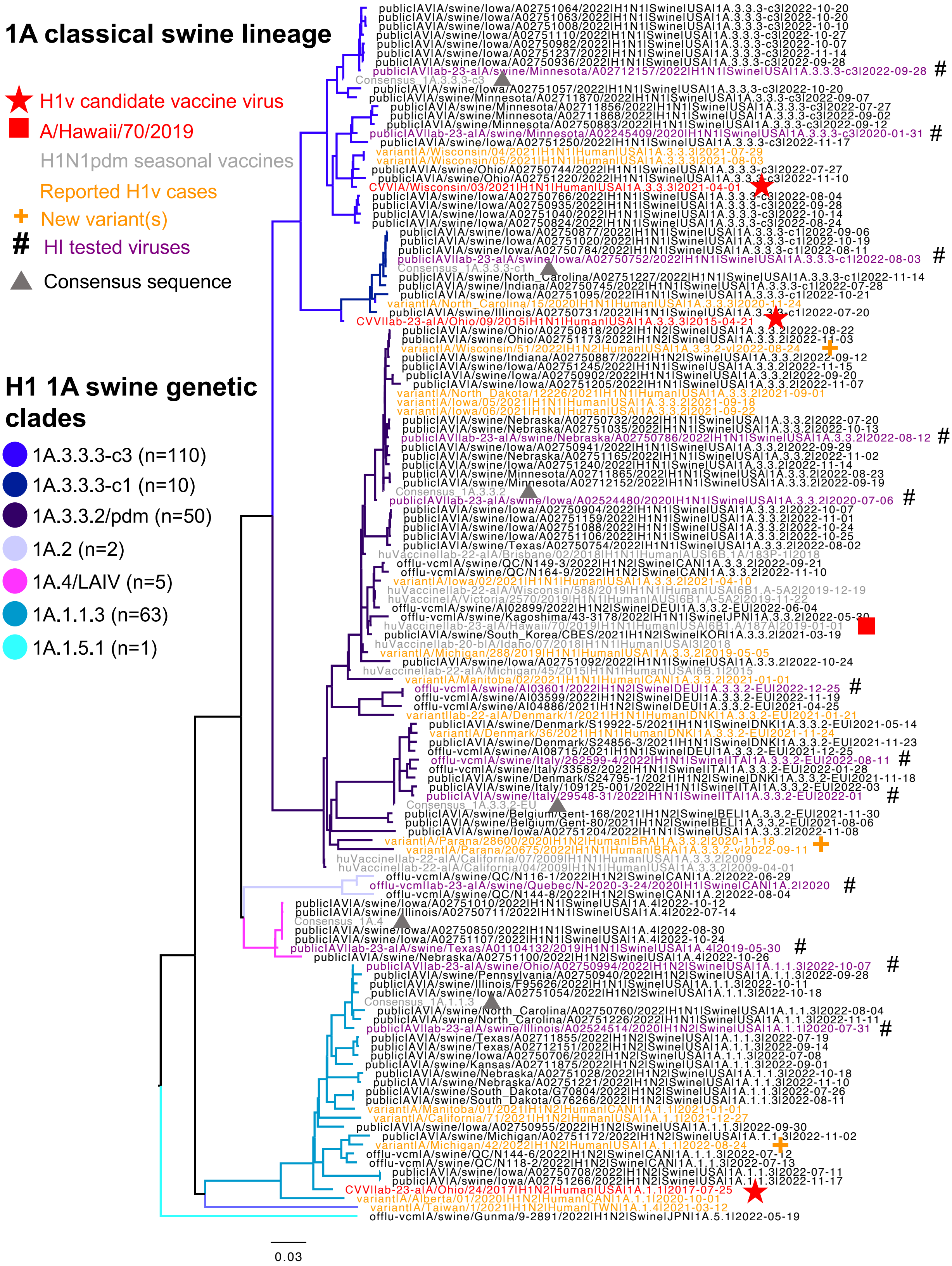


Figure 7. Swine H1 HA genes of the 1A lineage (tree was proportionally down-sampled to 100 swine HA genes, excluding references). Number of detections of each clade from data deposited between July 1 - December 31, 2022 are presented adjacent to the clade name in the figure key.

Antigenic analysis: Swine 1A Lineage

Table 1. USA Data: Hemagglutination inhibition of CVV or human seasonal vaccine ferret antisera against contemporary swine 1A lineage strains selected to represent clade consensus.

- > 8 fold reduction
- 8 fold reduction
- 4 fold reduction

	Global Clade	US Clade	**IDCDC-RG59 A/Ohio/24/2017-like CVV**	A/swine/Illinois/A02524514/2020 #26	A/swine/Illinois/A02524514/2020 #27	rg-A/Hawaii/70/2019 #9	rg-A/Hawaii/70/2019 #11	A/swine/Iowa/A02524480/2020*#30	A/swine/Iowa/A02524480/2020* #14	**A/Ohio/9/2015 CVVRG48A**	A/swine/Minnesota/A02245409/2020 #28	A/swine/Minnesota/A02245409/2020 #12	Human High responder	Human Low responder
IDCDC-RG59 A/Ohio/24/2017 CVV	1A.1.1.3	alpha-del	640	320	160	160	160	160	320	<10	20	20	80	20
A/swine/Illinois/A02524514/2020*	1A.1.1.3	alpha-del	<10	1280	1280	<10	<10	<10	10	<10	<10	<10	40	<10
A/swine/Ohio/A02750994/2022	1A.1.1.3	alpha-del	20	320	320	<10	<10	<10	<10	<10	<10	<10	10	<10
rg-A/swine/Quebec/N-2020-3-24/2020	1A.2	beta	20	<10	<10	1280	640	640	1280	10	20	20	640	40
rg-A/Hawaii/70/2019	6B.1A.5a.1	pdm09	10	<10	<10	1280	1280	1280	2560	10	20	10	1280	80
A/swine/Iowa/A02524480/2020*	1A.3.3.2	pdm09	20	<10	10	1280	640	640	1280	20	20	20	1280	80
A/swine/Nebraska/A02750786/2022	1A.3.3.2	pdm09	20	<10	<10	1280	1280	640	1280	10	<10	20	1280	80
A/Ohio/9/2015 CVV RG48A	1A.3.3.3	gamma.1	<10	<10	20	<10	10	40	20	320	40	20	320	10
A/swine/Iowa/A02750752/2022	1A.3.3.3-c1	gamma.1	<10	10	<10	<10	<10	<10	20	40	20	20	320	10
A/swine/Minnesota/A02245409/2020*	1A.3.3.3-c3	gamma.3	<10	<10	<10	10	10	40	40	20	640	640	640	40
A/swine/Minnesota/A02712157/2022	1A.3.3.3-c3	gamma.3	<10	<10	<10	<10	<10	20	20	40	320	160	640	20
A/swine/Texas/A01104132/2019	1A.4	gamma-2-beta-like	20	<10	<10	160	80	160	160	80	20	40	160	20

Reference CVV in red, seasonal vaccine strains in dark red, new swine strains in bold. Homologous titers highlighted in grey. *Previously tested; rg=synthetic HA/NA on PR8 backbone. Human sera were collected in USA with high or low responder relative to A/Hawaii/70/2019, pools of 2 male and 2 female adults in each.

- The contemporary swine 1A.1.1 (alpha-del) had >8-fold decrease from 1A.1.1 CVV A/Ohio/24/2017 ferret anti-sera and had significant decreases in titer in adult human sera.
- The 1A.2 swine strain was not significantly detected by any CVV or vaccine anti-sera but reacted with adult human sera.
- The contemporary swine 1A.3.3.2 (pdm) with onward transmission in swine retained cross-reactivity A/Hawaii/70/2019-like 6B.1A.5a.1 vaccine strain and with adult human sera.
- The contemporary swine 1A.3.3.3 (gamma) clade 1 virus had an 8-fold decrease with the within-clade 1A.3.3.3-clade 1 CVV A/Ohio/09/2015 and 4- to 8-fold reduction in adult human sera. The contemporary swine 1A.3.3.3 (gamma) clade 3 virus had an 8-fold decrease with the 1A.3.3.3-clade 1 CVV A/Ohio/09/2015 but retained reactivity with adult human sera.
- The swine 1A.4 (gamma-2-beta-like) virus had limited detection by any CVV or vaccine anti-sera and 4- to 8-fold decrease with the adult human sera.

Table 2. EU Data: Hemagglutination inhibition of CVV or human seasonal vaccine ferret antisera against contemporary swine 1A lineage strains.

- > 8 fold reduction
- 8 fold reduction
- 4 fold reduction

	Global Clade	A/California/7/2009	A/Ohio/9/2015 CVV
A/California/7/2009	H1N1 1A.3.3.2	80	20
A/Denmark/1/2021	1A.3.3.2	80	20
A/swine/Italy/29548-31/2022	1A.3.3.2	40	320
A/swine/Italy/262599-4/2022	1A.3.3.2	80	0
A/swine/Germany/AI03601/2022	1A.3.3.2	20	0
A/Ohio/9/2015 CVV	H1N1 1A.3.3.3	ND	ND

Reference seasonal vaccine strains in dark red, variant in orange, new swine strains in bold. Homologous titers highlighted gray. ND=not done.

- The contemporary swine 1A.3.3.2 (pdm) strains with onward transmission in European swine retained variable cross-reactivity to A/California/7/2009.

Table 3. Amino acid substitutions between representative swine 1A.1.1.3 clade strains compared to the within-clade CVV (A/Ohio/24/2017) and recent human variant.

site	A/Ohio/24/2017	A/swine/Illinois/A02524514/2020	A/swine/Ohio/A02750994/2022	A/Michigan/42/2022	annotations
43	K			R	
48	A	S	S		
84	N			T	
126	H		Y	Y	
127	K			E	
132	V	E	E		RBS
138	D	Y	Y	Y	
141	A	Q	K	Q	
149	I	M	M	M	
155	G	D	A		Sa
156	N	D	D	D	Sb
170	R	G	G		Ca1
185	G			D	
189	Q			K	Sb, RBS
193	Q			H	Sb, RBS
204	S			P	Ca1
209	E	K	K	K	
216	T			K	
224	T	A	A		RBS
230	Y			H	
234	V			I	
252	K	R	R		
264	G			S	
270	A			T	
310	T	R	R	K	
311	K	R	R	R	
aadiff		13	14	20	

Reference CVV in red, HI swine strains in purple, new variant detection in orange.

Table 4. Amino acid substitutions between 1A.2 compared to the nearest human H1 vaccine (A/Hawaii/70/2019) and the most similar vaccine (A/California/07/2009).

Relative to HI

site	A/Hawaii/70/2019	A/swine/Quebec/N-2020-3-24/2020	annotations
35	D	N	
61	I	L	
71	S	F	Cb
73	A	R	Cb
83	S	P	
85	S	P	
104	Q	H	
109	S	L	
120	T	A	
121	S	N	
128	S	T	
129	D	N	
137	P	S	Ca2
138	H	Y	
142	K	N	Ca2
162	N	S	Sa
163	Q	K	Sa
164	T	S	Sa
168	D	N	
170	G	K	Ca1
176	L	I	
185	I	S	
186	A	T	
187	A	D	RBS
189	E	Q	Sb, RBS
190	S	T	Sb, RBS
195	A	E	Sb, RBS
203	T	S	
205	R	K	
216	T	A	
224	E	A	RBS
234	V	I	
235	E	D	
239	K	T	
256	T	A	
260	D	G	
261	A	S	
270	T	K	
273	H	Q	
274	D	N	
276	N	T	
283	E	K	
285	A	S	
295	V	I	
298	I	V	
302	K	E	
311	K	N	
314	L	M	
321	V	I	
aadiff		49	

Relative to most similar vaccine

site	A/California/07/2009	A/swine/Quebec/N-2020-3-24/2020	annotations
35	D	N	
61	I	L	
71	S	F	Cb
73	A	R	Cb
74	S	R	Cb
84	S	N	
85	S	P	
97	D	N	
104	Q	H	
109	S	L	
120	T	A	
121	S	N	
128	S	T	
137	P	S	Ca2
138	H	Y	
142	K	N	Ca2
168	D	N	
170	G	K	Ca1
176	L	I	
183	S	P	
186	A	T	
190	S	T	Sb, RBS
195	A	E	Sb, RBS
205	R	K	
216	I	A	
224	E	A	RBS
234	V	I	
235	E	D	
239	K	T	
260	N	G	
261	A	S	
270	T	K	
273	H	Q	
274	D	N	
276	N	T	
285	A	S	
298	I	V	
302	K	E	
311	K	N	
314	L	M	
aadiff		40	

Reference vaccine strain in gray, HI swine strains in purple.

Table 5. Amino acid substitutions between representative swine 1A.3.3.2 clade strains compared to a human seasonal H1 vaccine strain (A/Idaho/07/2018) used in HI assays and recent human variants.

site	A/Idaho/07/2018	A/swine/Iowa/A02524480/2020	A/swine/Nebraska/A02750786/2022	A/swine/Italy/29548-31/2022	A/swine/Italy/262599-4/2022	A/swine/Germany/AI03601/2022	A/Parana/20675/2022	A/Wisconsin/51/2022	annotations
15	T		N						
19	V			I	I		I		
25	T				S				
43	K			Q	Q				
47	V		I					I	
51	H		N			Q		N	
69	S			P	P				
70	L			T	I				Cb
74	R			G	G	S			Cb
82	T			A	A				
83	S						P		
84	N			S	S	S	S		
85	S		P	P	P			P	
94	D				N				
97	N			D	D		E		
104	Q			H	H				
113	R	K							
119	K			N	N				
120	T			A	A		S		
125	N					D	D		Sa
126	H					N			
127	D					K			
128	S					L	A		
129	N			S	S	K			
130	K					E	N		
132	V					K			RBS
135	A					S	S		RBS
137	P	S	S					S	Ca2
139	A			N	N	N			
141	A						T		
142	K			N	N	S	S		Ca2
152	V			I	I		I		
154	K					E			
155	G			E	E	K			Sa
156	N					D			Sb
157	S					P		L	Sa
160	K					M			Sa
162	N			S			S		Sa
163	Q			I	I	I	K		Sa

site	A/Idaho/07/2018	A/swine/Iowa/A02524480/2020	A/swine/Nebraska/A02750786/2022	A/swine/Italy/29548-31/2022	A/swine/Italy/262599-4/2022	A/swine/Germany/AI03601/2022	A/Parana/20675/2022	A/Wisconsin/51/2022	annotations
164	T			S	S	S	S		Sa
166	I			A	V				Ca1
168	D					N			
170	G				E				Ca1
173	V	I	I					I	
176	L			V	V				
185	T			N	N	A	N	I	
186	A			N	D	D	T		
187	D			S	S	S	S		RBS
189	Q						Y		Sb, RBS
190	S			W	W	W			Sb, RBS
194	N			D	D				RBS
195	A						G		Sb, RBS
196	D			N	N				
205	R		K	K	K			K	
209	K					M			
216	T			K	R	R	I		
222	D					N	N		Ca2, RBS
224	E				D				RBS
250	V			A	A	M			
256	T			A	A	A	A		
260	N					H			
261	A			T	T	V			
270	T			A	A	A			
272	V			I	I	I			
274	D			N	N			N	
283	E			K	K	K	K		
295	V			I	I	I	I		
302	K				R	Q	Q		
308	K			R	R				
311	K			R					
321	V			T	T	D			
324	I						V		
aa diff		3	7	41	44	38	27	9	

Reference vaccine strain in gray, HI strains in purple, new variants detection in orange.

Table 6a. Amino acid substitutions between a representative swine 1A.3.3.3-clade 1 strain compared to the within-clade CVV (A/Ohio/09/2015 RG48A) used in the HI assay.

site	A/Ohio/09/2015	A/swine/Iowa/A02750752/2022	annotations
22	K	R	
48	X	A	
68	E	D	
72	T	R	
82	T	N	
83	S	P	
120	T	N	
125	N	K	Sa
169	R	K	
194	N	H	RBS
204	S	P	Ca1
205	R	K	
222	G	D	Ca2, RBS
228	N	S	
235	E	A	
269	E	G	
278	T	I	
283	N	S	
295	I	V	
aadiff		19	

Reference CVV in red, HI swine strain in purple.

Table 6b. Amino acid substitutions between 1A.3.3.3-clade 3 compared to the nearest available human H1 CVV in HI (A/Ohio/09/2015) and the most similar CVV (A/Wisconsin/03/2021).

Relative to HI

site	A/Ohio/09/2015	A/swine/Minnesota/A02245409/2020	A/swine/Minnesota/A02712157/2022	annotations
2	K	T	T	
3	I	L	L	
36	K	R	R	
48	X	A	A	
56	N		S	
71	A	S	S	Cb
74	S		R	Cb
83	S	P		
84	S	N	K	
86	N	E	E	
113	K	R	R	
120	T	A		
127	E	D	D	
130	K	R		
137	P	S		Ca2
146	K	R	R	
149	I	V	V	
153	K	Q	Q	Sb
155	E	G	G	Sa
161	I	V		
163	I	K	K	Sa
166	T	I	I	Ca1
168	N		D	
169	R		K	
170	G	E	E	Ca1
171	K		R	
183	P	S	S	
186	T	A	A	
193	Q	K	K	Sb, RBS
196	N	D	D	
197	S	A	A	
205	R	K	K	
222	G	D	D	Ca2, RBS
250	V	A	A	
252	R		I	
262	G		E	
269	E	D	D	
271	P	S	S	
278	T		A	
295	I		V	
302	E		K	
326	S		T	
aadiff		31	37	

Relative to most similar CVV

site	A/Wisconsin/03/2021	A/swine/Minnesota/A02245409/2020	A/swine/Minnesota/A02712157/2022	annotations
35	T	N	N	
45	K	R	R	
56	N		S	
74	S		R	Cb
83	S	P		
84	N		K	
120	T	A		
127	E	D	D	
129	D	N	N	
130	K	R		
137	P	S		Ca2
142	R	N	N	Ca2
161	V		I	
163	T	K	K	Sa
168	N		D	
169	K	R		
171	K		R	
189	R	Q	Q	Sb, RBS
195	E	A	A	Sb, RBS
205	R	K	K	
224	S	A	A	RBS
252	R		I	
262	G		E	
270	A	T	T	
278	T		A	
295	I		V	
302	E		K	
326	S		T	
aadiff		16	23	

Reference CVV in red, HI swine strains in purple.

Table 7. Amino acid substitutions between 1A.4 compared to the human H1 vaccine (A/Hawaii/70/2019) used in USA HI assays and the most similar vaccine (A/California/07/2009).

Relative to HI

site	A/Hawaii/70/2019	A/swine/Texas/A01104132/2019	annotations
35	D	E	
40	K	R	
71	S	F	Cb
73	A	T	Cb
74	R	S	Cb
119	K	N	
120	T	A	
126	H	Y	
127	D	E	
128	S	T	
129	D	S	
130	K	R	
138	H	Y	
142	K	N	Ca2
146	K	R	
149	I	L	
162	N	S	Sa
163	Q	K	Sa
164	T	S	Sa
168	D	N	
170	G	E	Ca1
183	P	S	
185	I	S	
186	A	T	
187	A	D	RBS
189	E	Q	Sb, RBS
203	T	S	
205	R	K	
224	E	A	RBS
239	K	T	
256	T	A	
258	E	K	
260	D	G	
261	A	S	
271	P	S	
278	T	N	
283	E	K	
295	V	I	
298	I	V	
302	K	E	
310	T	K	
314	L	M	
321	V	I	
aadiff		43	

Relative to most similar vaccine

site	A/California/07/2009	A/swine/Texas/A01104132/2019	annotations
35	D	E	
40	K	R	
71	S	F	Cb
73	A	T	Cb
84	S	N	
97	D	N	
119	K	N	
120	T	A	
126	H	Y	
127	D	E	
128	S	T	
129	N	S	
130	K	R	
138	H	Y	
142	K	N	Ca2
146	K	R	
149	I	L	
168	D	N	
170	G	E	Ca1
186	A	T	
205	R	K	
216	I	T	
224	E	A	RBS
239	K	T	
258	E	K	
260	N	G	
261	A	S	
271	P	S	
278	T	N	
298	I	V	
302	K	E	
310	T	K	
314	L	M	
321	V	I	
aadiff		34	

Reference human seasonal vaccine in gray, HI swine strain in purple.

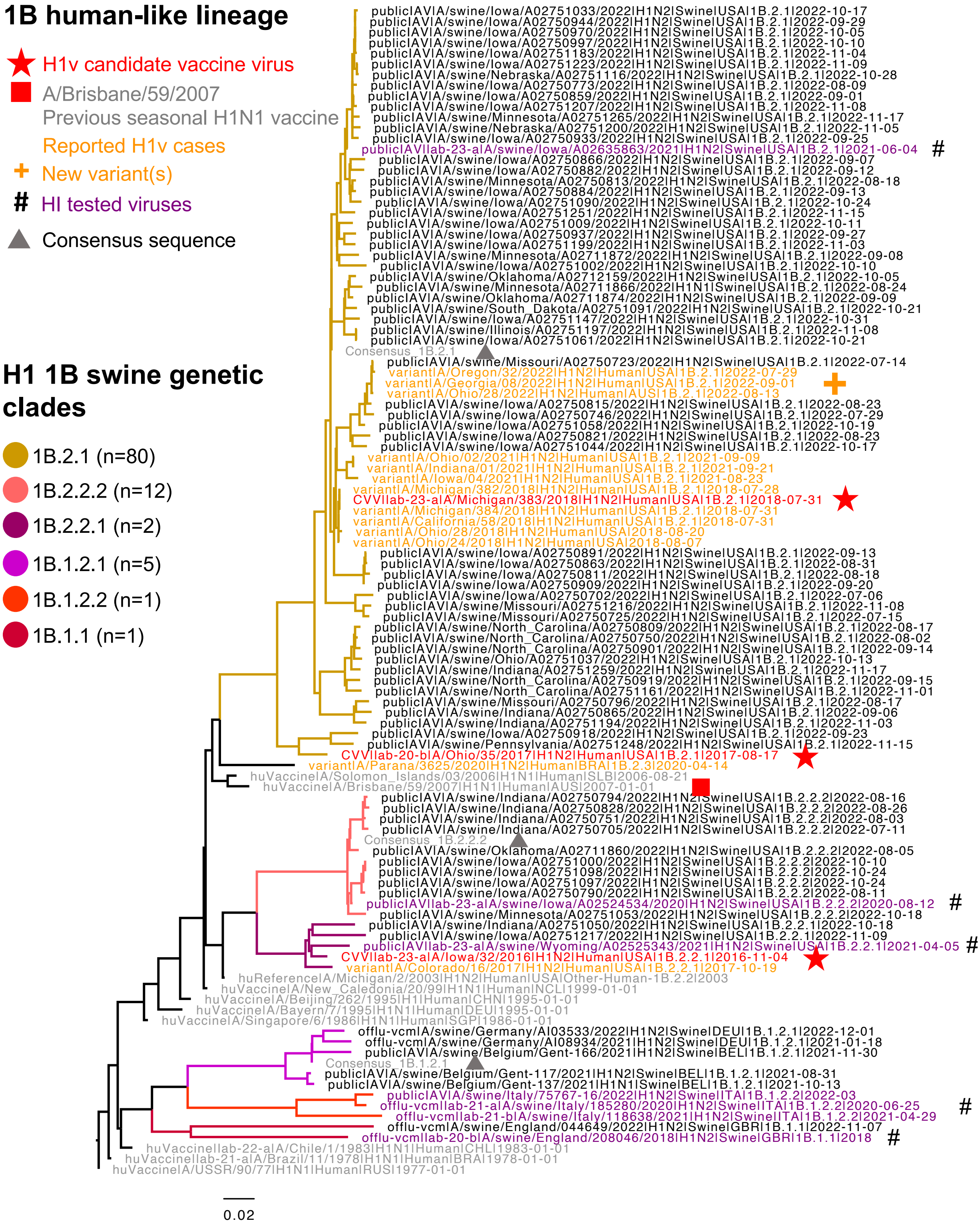


Figure 8. Swine H1 HA genes of the 1B lineage (tree was proportionally down sampled to 59 swine HA genes, excluding references). Number of detections of each clade from data deposited between July 1 - December 31, 2022 are presented adjacent to the clade name in the figure key.

Antigenic analysis: Swine 1B Lineage

Table 8. USA Data: Hemagglutination inhibition of CVV vaccine ferret antisera against contemporary swine 1B lineage strains selected to represent clade consensus.

- > 8 fold reduction
- 8 fold reduction
- 4 fold reduction

	Global Clade	US Clade	**A/Michigan/383/2018 RG58A**	**A/Iowa/32/2016**	A/swine/Wyoming/A02525343/2021** #15	A/swine/Wyoming/A02525343/2021* #16	Human High responder	Human Low responder
A/Michigan/383/2018 RG58A	1B.2.1	delta-2	80	<10	<10	<10	10	20
A/swine/Iowa/A02635863/2021	1B.2.1	delta-2	80	<10	<10	<10	10	20
A/Iowa/32/2016	1B.2.2.1	delta-1a	<10	320	40	20	80	40
A/swine/Wyoming/A02525343/2021**	1B.2.2.1	delta-1a	<10	20	160	160	40	20
A/swine/Iowa/A02524534/2020*	1B.2.2.2	delta-1b	<10	10	<10	<10	20	10

Reference CVV in red, new swine strains in bold. Homologous titers highlighted grey. *Previously tested in report 2021a; **Previously tested in report 2022b. Human sera were collected in USA with high or low responder relative to A/Hawaii/70/2019, pools of 2 male and 2 female adults in each.

- The contemporary swine 1B.2.1 (delta-2) had no loss of titer to the within-clade CVV A/Michigan/383/2018 but limited titers in adult human sera.
- The 1B.2.2.1 A/swine/Wyoming/A02525343/2021 had a >8-fold reduction from the within clade CVV A/Iowa/32/2016 and limited titers in adult human sera.
- The contemporary swine 1B.2.2.2 (delta-1b) does not have a CVV contained within clade and had a significant greater than 8-fold decrease from CVV A/Iowa/32/2016 and limited titers in adult human sera.

Table 9. UK & EU Data: Hemagglutination inhibition of CVV vaccine ferret antisera against contemporary swine 1B lineage strains selected to represent clade consensus.

	Global Clade	**A/Michigan/383/2018 RG58**	**A/Chile/1/1983**
A/Michigan/383/2018 RG58A*	1B.2.1 d2	160	1280
A/Chile/1/1983*	H1 seasonal	160	1280
A/swine/England/208046/2018*	1B.1.1	ND	80
A/swine/Italy/118638/2021*	1B.1.2.2	20	40
A/swine/Italy/185280/2020*	1B.1.2.2	ND	40

- > 8 fold reduction
- 8 fold reduction
- 4 fold reduction

Reference CVV in red, seasonal vaccine strains in dark red, new swine strains in bold. Homologous titers highlighted in gray. ND=not done. *Previously tested in report 2022b

- There are no within-clade CVVs for 1B lineages from Europe.
- The swine 1B.1.1 had significant loss in cross-reactivity with A/Chile/1/1983.
- The contemporary swine 1B.1.2.2 had significant decrease in cross reactivity against both the 1B.2.1 d2 CVV and against the human seasonal reference strain.

Table 10. Amino acid substitutions between a representative swine 1B.2.1 strain compared to the within-clade CVV (A/Michigan/383/2018 RG58A) and recent human variants.

site	A/Michigan/383/2018	A/swine/Iowa/A02635863/2021	A/Ohio/28/2022	A/Oregon/32/2022	A/Georgia/08/2022	annotations
36	S		R	R	R	
71	N	T	T	T	T	Cb
102	R		K			
113	K		R	R	R	
149	L	V				
169	E		K	K	K	
170	G	E				Ca1
173	V	I				
199	V		I	I	I	
205	H		Y	Y	Y	
215	A		V	V	V	
224	E		G	G	G	RBS
260	S	G				
261	F	S				
276	N		D	D	D	
aadiff		6	10	9	9	

Reference CVV strain in red, HI swine strain in purple, new variant detections in orange.

Table 11. Amino acid substitutions between a representative swine 1B.2.2.1 strain compared to the most similar CVV (A/Iowa/32/2016 1B.2.2.1).

site	A/Iowa/32/2016	A/swine/Wyoming/A02525343/2021	annotations
19	L	V	
72	S	P	
74	K	E	Cb
96	T	A	
106	S	N	
130	T	D	
132	K	T	RBS
157	L	R	Sa
168	E	D	
175	I	V	
208	R	K	
215	T	A	
222	D	N	Ca2, RBS
241	I	V	
287	N	T	
310	T	R	
aadiff		16	

Reference CVV strain in red, HI swine strain in purple.

Table 12. Amino acid substitutions between a representative swine 1B.2.2.2 strain compared to the most similar human strain (A/Michigan/2/2003).

site	A/Michigan/2/2003	A/swine/Iowa/A02524534/2020	annotations
2	T	M	
50	L	I	
69	L	S	
74	E	K	Cb
94	Y	D	
129	V	T	
132	V	K	RBS
141	K	E	
142	S	G	Ca2
149	L	V	
153	G	E	Sb
162	I	S	Sa
166	A	K	Ca1
176	L	I	
184	N	D	
186	G	E	
187	D	N	RBS
193	H	R	Sb, RBS
194	T	K	RBS
202	V	A	
208	R	E	
222	D	N	Ca2, RBS
228	N	K	
236	P	A	
249	I	V	
256	A	T	
261	F	L	
271	P	S	
273	D	N	
274	E	K	
277	A	T	
314	M	L	
aadiff		32	

Reference human seasonal vaccine in gray, HI swine strain in purple.

Table 13. Amino acid substitutions between representative swine 1B.1.X strains compared to the most similar human seasonal vaccine A/Chile/1/1983 used in HI assays.

site	A/Chile/1/1983	A/swine/Italy/185280/2020|1B.1.2.2	A/swine/Italy/118638/2021|1B.1.2.2	A/swine/England/208046/2018|1B.1.1	annotations
19	V			I	
35	D	N		N	
36	N	S		S	
44	L			M	
47	I	V	V		
54	K		R		
70	L			S	Cb
71	F		L		Cb
73	K			R	Cb
82	T	P	A		
85	S	A	A	P	
89	T	L	L	I	
94	Y		H		
96	A	S	S	S	
109	S	A			
111	F		I	V	
116	I			M	
124	P	S			Sa
127	N	S	S		
128	V		I		
129	T	-	-		
130	K	-	-	R	
132	V	S	A	K	RBS
134	A			V	RBS
135	A	S	S	S	RBS
137	S	P			Ca2
138	H	K	K		
139	K	Q	Q	N	
141	K		R		
142	S		R		Ca2
146	R	T	T	K	
155	N			D	Sa
157	S			L	Sa
161	L			I	
162	S	T	T		Sa
163	K	M	M	N	Sa
164	S			H	Sa
166	V	M	M		Ca1
168	N	D	D		
170	E		K		Ca1
171	K	R	R		
176	L			I	
181	H			N	
184	N		S		
185	I	M		M	
187	D			N	RBS
189	K	R	R	R	Sb, RBS
190	T	A	A	A	Sb, RBS
196	N	T	T	T	
202	V	M	T		
205	H	Q			
208	R		K		
209	R		K		
211	T	A			
215	A			E	
220	V	I	I	I	RBS
222	N		D		Ca2, RBS
235	E	D			
237	G	R	S		Ca1
238	D			E	
241	I	T			
248	L			F	
249	I	V			
258	S	K	N		
261	F			L	
262	G	E	E	R	
267	T	V	V	I	
268	S			T	
270	A		V		
276	D		N		
277	A			T	
278	K		T	E	
283	Q		R		
288	S	N	N	N	
295	V		I		
298	V		I		
299	T			A	
307	V			I	
308	R	K	K	K	
310	T	A			
311	K			R	
313	R	K	K		
315	V	A	A		
aadiff		43	49	44	

Reference CVV strain in red, HI swine strain in purple.

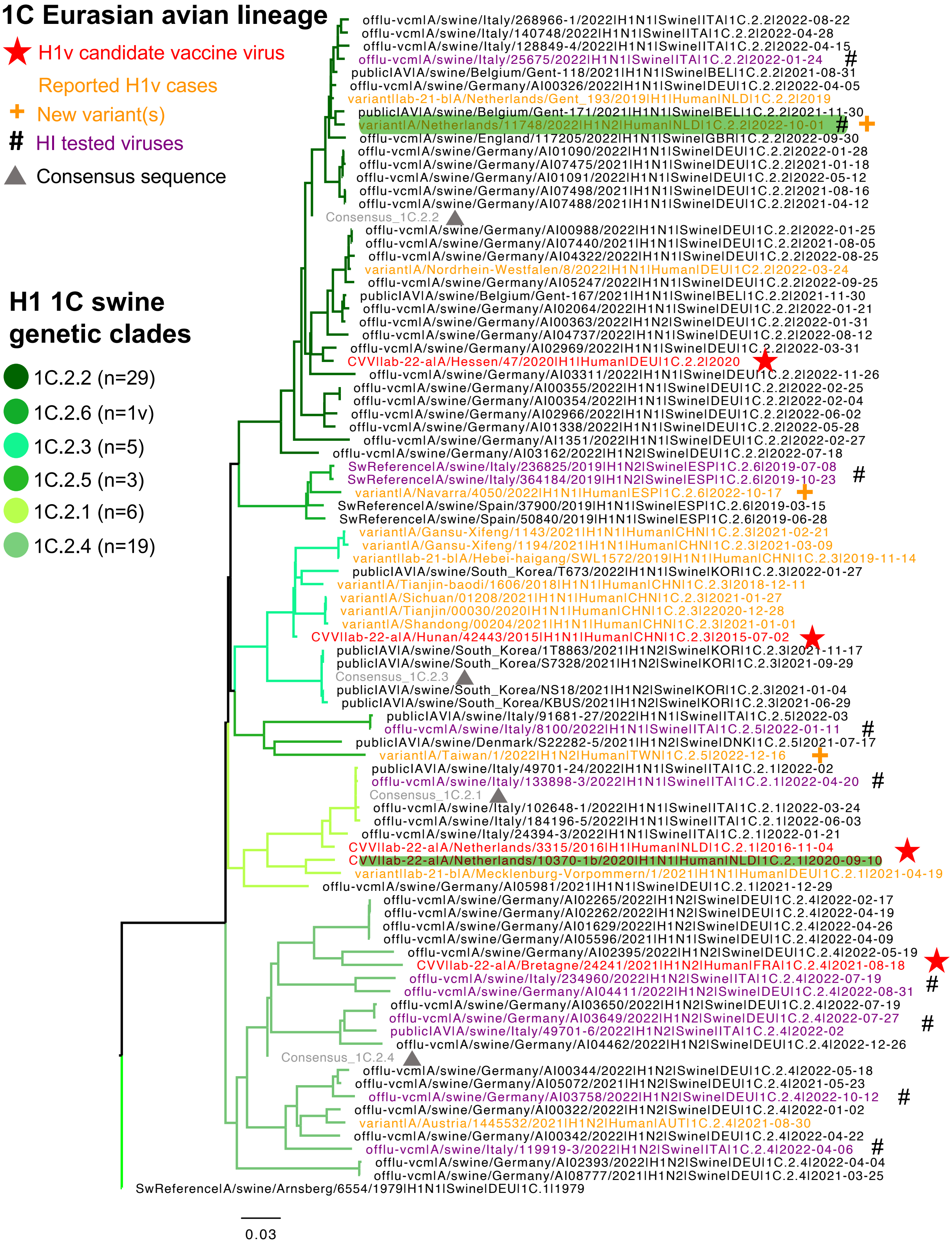


Figure 9. Swine H1 HA genes of the 1C lineage. Number of detections of each clade from data deposited between July 1 - December 31, 2022 are presented adjacent to the clade name in the figure key.

Antigenic analysis: Swine 1C Lineage

Table 14. UK & EU Data: Hemagglutination inhibition of CVV vaccine ferret antisera against contemporary swine 1C lineage strains selected to represent clade consensus.

- > 8 fold reduction
- 8 fold reduction
- 4 fold reduction

	Global Clade	A/Netherlands/3315/2016 CVV	A/Netherlands/10370-1b/2020 CVV	A/Hessen/47/2020-like CVV	A/Hunan/42443/2015 CNIC-1601 CVV	A/Bretagne/24241/2021 CVV
A/Netherlands/3315/2016 CVV	1C.2.1	ND	ND	ND	ND	ND
A/Netherlands/10370-1b/2020 CVV	1C.2.1	320	640	320	320	40
A/swine/Italy/133898-3/2022|H1N1	**1C.2.1**	640	640	160	80	<20
A/Hessen/47/2020-like CVV	1C.2.2	640	640	2560	2560	20
A/swine/Italy/25675/2022	**1C.2.2**	160	320	1280	1280	20
A/Netherlands/11748/2022	**1C.2.2**	ND	ND	ND	ND	ND
A/Hunan/42443/2015 CNIC-1601 CVV	1C.2.3	320	640	1280	2560	80
A/Bretagne/24241/2021 CVV	1C.2.4	160	20	80	80	2560
A/swine/Italy/49701-6/2022|H1N2	**1C.2.4**	160	80	40	80	80
A/swine/Italy/234960/2022|H1N2	**1C.2.4**	20	20	20	40	20
A/swine/Italy/119919-3/2022|H1N2	**1C.2.4**	80	80	20	80	20
A/swine/Germany/AI04411/2022	**1C.2.4**	40	20	20	<10	<10
A/swine/Germany/AI03758/2022	**1C.2.4**	80	40	20	<10	<10
A/swine/Germany/AI03649/2022	**1C.2.4**	80	80	80	<10	<10
A/swine/Italy/8100/2022	**1C.2.5**	160	160	160	160	2560
A/swine/Italy/236825/2019	**1C.2.6**	80	80	40	20	20
A/swine/Italy/364184/2019	**1C.2.6**	40	40	40	20	20

Reference CVV in red, seasonal vaccine strains in gray, new swine strains in bold, variant in orange. Homologous titers highlighted in gray. ND=not done.

- The 1C.2.1 swine strain retained reactivity to the within clade CVV.
- The 1C.2.2 swine strain retained cross-reactivity with the within clade CVV.
- The 1C.2.4 swine strains displayed >8-fold reduction to the within clade CVV.
- The 1C.2.5 swine strain has no within clade CVV but reacted to the 1C.2.4 CVV.
- The 1C.2.6 swine strains have no within clade CVV and had limited cross-reactivity to CVV in other 1C clades.

Table 15. Amino acid substitutions between a representative swine 1C.2.1 strain compared to the within-clade CVV (A/Netherlands/3315/2016).

site	A/Netherlands/3315/2016	A/swine/Italy/133898-3/2022	annotations
20	M	L	
48	A	P	
71	I	T	Cb
89	A	T	
120	E	A	
141	I	V	
155	E	N	Sa
175	I	V	
215	V	A	
227	M	I	
321	T	I	
326	S	T	
aadiff		12	

Reference CVV in red, HI swine strain in purple.

Table 16. Amino acid substitutions between representative swine 1C.2.2 strains compared to the within-clade CVV (A/Hessen/47/2020 CVV) and recent human variant.

site	A/Hessen/47/2020	A/swine/Italy/25675/2022	A/Netherlands/11748/2022	annotations
3	I	L	L	
53	K	R	R	
66	E	D		
84	D	N	N	
89	T		I	
97	D	N	N	
118	P	S		
120	A	S		
121	T	S		
125	N	D	D	Sa
142	N		K	Ca2
151	I		V	
161	L	I	I	
163	N	K	K	Sa
175	V	I		
185	D	E	E	
190	T		A	Sb, RBS
209	R		K	
214	T	I	V	
235	D	N	N	
238	D		E	
253	Y	H	H	
267	M	I		
269	N	D	D	
302	E	K	K	
aadiff		19	19	

Reference CVV in red, HI swine strains in purple, new variant detection in orange.

Table 17. Amino acid substitutions between representative swine 1C.2.4 strains compared to the within-clade CVV (A/Hunan/42443/2015).

site	A/Hunan/42443/2015	A/swine/Italy/234960/2022	A/swine/Italy/119919-3/2022	A/swine/AI04411/2022	A/swine/AI03758/2022	A/swine/AI03649/2022	A/swine/Italy/49701-6/2022	annotations
5	V	I		I				
31	N	D				D	D	
35	N	T	T	T	T	T	T	
46	G			E				
48	I	A	A	A	A	A	A	
51	Q	N		N	K			
53	G				E			
56	S	N	N	N	N	N	N	
66	K	E	E	E	E	E	E	
69	L			V				
70	L	I						Cb
83	S				P	P		
84	N	D		D				
86	K		E		D			
89	A	T	T	T	T	I	I	
94	E				K			
96	A		S			S	S	
102	K		R		R	R		
104	Q	L		L		L	L	
106	S						G	
107	T						A	
112	E	K		K				
116	I		V		M		V	
119	K	E		E		G	E	
121	T					A		
124	P	S				E	K	Sa
125	N		E		D			Sa
127	D	-	E	-	E	-	-	
128	T					E	E	
130	R	G		G	-	K	K	
132	T			A				RBS
134	V			A	I	G		RBS
135	A	S		S		S	S	RBS
137	S		Y					Ca2
138	H					R	R	
141	A			G		T	T	
142	N	S		K	R	R	P	Ca2
146	R					Q	Q	
149	L	S		S				
152	V	T		T	L	T	T	
153	K		G		R			Sb
155	G		E			-	-	Sa
156	N	S		T			I	Sb
161	L					I	I	
163	K	R		R				Sa
168	N	D	D			D		
169	K	Q		Q		R		
170	G			E				Ca1
172	E					K	K	
175	V		I					
184	T		N					
185	D	A	Y		Y	Y	Y	
186	S		R		N			
189	Q	L		L				Sb, RBS
190	T		A			A	A	Sb, RBS
193	Q	Y						Sb, RBS
194	N					S	S	RBS
196	H	D						
199	V				I			
200	S	L						
202	G	A	E	A	E	V	V	
203	S					T	T	
205	K				N			
208	K	R	R		R	Q	Q	
211	T	K						
215	V		A					
216	A	T	T	T	T	E	D	
220	V	I	I	I	I	I	I	RBS
235	D				T			
239	T					N	N	
241	T			A				
249	I		V					
252	W	R		R		K	K	
253	H		Y		Y	Y	Y	
256	A						V	
258	K	S	N	S	D	D	D	
259	K					M	M	
260	G					S	S	
261	S		L		L			
262	S	I						
266	M		V		V		L	
267	R	K	K	K	I	K	K	
269	D				E			
271	Q	H	H		H	H	H	
283	H						Q	
288	G	S		S		S		
289	N			D			S	
290	L	R		R		R	R	
298	V	I		I	I	I	I	
311	Q				K			
324	I			L				
aa diff		42	32	39	37	47	48	

Reference CVV in red, HI swine strains in purple.

Table 18. Amino acid substitutions between representative swine 1C.2.5 strain compared to HI tested CVVs (A/Bretagne/24241/2021 and A/Netherlands/3315/2016) and recent human variant.

site	A/Bretagne/24241/2021	A/Netherlands/3315/2016	A/swine/Italy/8100/2022	A/Taiwan/1/2022	annotations
2	T		I		
5	I	V	V	V	
20	M		L	L	
35	T	N	N	N	
36	N	S	S	S	
44	L		M		
47	K		N	R	
51	Q			H	
53	G			R	
56	D	N		N	
69	L		F		
71	V	I	L	L	Cb
72	T			K	
80	I			V	
82	T		A		
83	S			P	
85	S		P		
89	T	A	A	I	
94	E		K		
104	L	Q	Q	Q	
111	F		L		
120	-	E	R	T	
121	N	T	T	T	
125	S	N	D	N	Sa
127	E			D	
128	A	T	T	T	
129	-	T	T	T	
130	-	K	K	K	
132	T	S			RBS
134	V		S		RBS
135	S	A		A	RBS
137	S			P	Ca2
138	K	H	H	H	
141	A	I		T	
142	N	K			Ca2
152	T	V	V	V	
153	S	K	K	K	Sb
155	G	E			Sa
156	K	N	N	N	Sb
157	P	S	S	S	Sa
159	S	P	P	P	Sa
161	L	I			
162	S		N		Sa
163	K	T			Sa
166	K	T	I	T	Ca1
168	N			D	
169	K		R		
175	V	I			
183	P		S		
184	T		N		
185	Y	D	D	D	
186	S		N		
190	T		A		Sb, RBS
202	V	G	G	G	
208	Q	K	R	R	
211	T			K	
215	V		M		
216	P	A	A	T	
219	E	K	K	K	RBS
220	I	V	V		RBS
221	R			N	Ca2, RBS
222	E		N		Ca2, RBS
224	R	A	A	A	RBS
227	M		I		
237	E	G	G	G	Ca1
245	T		N	N	
252	R	W	W	W	
253	Y			H	
258	E	N	K	N	
261	S			P	
262	N		S	S	
266	M			I	
267	K	M	I	T	
271	H	N			
273	H			Y	
283	H			Y	
287	K		N		
288	S		N		
289	D	N	S	N	
290	R	L	L	L	
295	V			I	
310	T		K		
321	I	T	V		
324	I	V			
aadiff		44	57	54	

Reference CVVs in red, HI swine strain in purple, new variant detection in orange.

Table 19. Amino acid substitutions between representative swine 1C.2.6 strains compared to HI tested CVV (A/Netherlands/3315/2016) and recent human variant.

site	A/Netherlands/3315/2016	A/swine/Italy/236825/2019	A/swine/Italy/364184/2019	A/Navarra/4050/2022	annotations
20	M	L	L	L	
47	K			R	
51	Q	H	H	H	
53	G	R	R	R	
71	I	L	L	L	Cb
72	T	K	K	K	
80	I	V	V	V	
83	S	P	P	P	
89	A	I	I	I	
120	E	A	A	T	
122	S	A	A		
127	E	D	D	D	
130	K	R	R		
132	S	T	T	T	RBS
137	S	P	P	P	Ca2
141	I	T	T	T	
142	K	N	N	N	Ca2
155	E	G	G	G	Sa
161	I	L	L	L	
163	T	N	N	K	Sa
168	N			D	
175	I	V	V	V	
199	V	I	I		
208	K	R	R	R	
211	T	K	K	K	
216	A	T	T	T	
220	V	I	I	I	RBS
221	R	S	S	N	Ca2, RBS
235	D	N	N		
245	T	N	N	N	
253	Y			H	
261	S			P	
262	N			S	
266	M	I	I	I	
267	M	T	T	T	
269	D		E		
271	N	H	H	H	
273	H	Y	Y	Y	
283	H	Y	Y	Y	
295	V			I	
321	T	I	I	I	
324	V	I	I	I	
aadiff		35	36	37	

Reference CVV in red, HI swine strains in purple, new variant detection in orange.

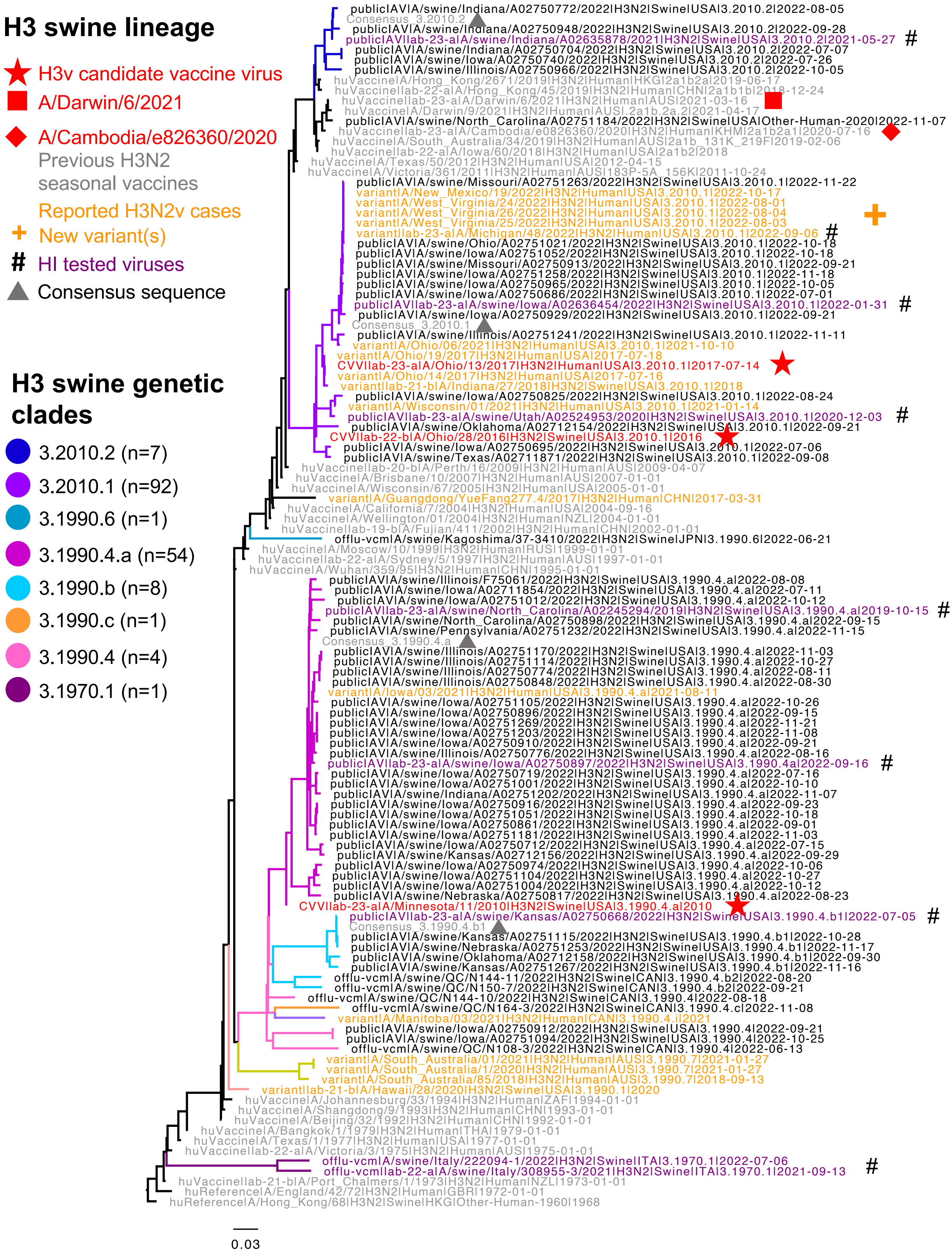


Figure 10. Swine H3 HA genes. Number of detections of each clade from data deposited between July 1 - December 31, 2022 are presented adjacent to the clade name in the figure key. Clades within the tree were proportionally down sampled to 64 swine HA genes (excluding references); tree includes clade consensus sequences, and human vaccine strains.

Antigenic analysis: Swine H3

Table 19. USA Data: Hemagglutination inhibition of CVV or human seasonal vaccine ferret antisera against contemporary swine H3 strains selected to represent clade consensus.

- > 8 fold reduction
- 8 fold reduction
- 4 fold reduction

	Global Clade	A/Minnesota/11/2010 x 203	A/swine/North Carolina/A02245294/2019 (H3N2) #32	A/swine/North Carolina/A02245294/2019 (H3N2) #18	IDCDC-RG55C A/Ohio/28/2016-like CVV	IDCDC-RG60A A/Ohio/13/2017 CVV	A/swine/Utah/A02524953/2020 (H3N2) #19	A/swine/Utah/A02524953/2020 (H3N2) #20	rg-A/Cambodia/e826360/2020 (H3N2)-like #1	rg-A/Cambodia/e826360/2020 (H3N2)-like #25	rg-A/Darwin/6/2021 (H3N2)-like #5	rg-A/Darwin/6/2021 (H3N2)-like #6	Human High H3 responder	Human Low H3 responder
A/Minnesota/11/2010 x 203	1990.4.a	640	80	160	20	20	40	80	<10	<10	80	10	80	20
A/swine/NorthCarolina/A02245294/2019*	1990.4.a	80	640	640	10	20	20	40	20	40	40	10	160	80
A/swine/Iowa/A02750897/2022	1990.4.a	40	320	320	<10	40	20	40	20	20	20	<10	160	80
A/swine/Kansas/A02750668/2022	1990.4.b1	<10	<10	10	<10	<10	<10	10	<10	<10	10	<10	320	160
ID40CDC-RG55C A/Ohio/28/2016-like CVV	2010.1	20	40	40	2560	320	160	320	40	40	40	20	320	80
IDCDC-RG60A A/Ohio/13/2017 CVV	2010.1	<10	20	80	80	1280	160	160	<10	10	20	10	320	80
A/swine/Iowa/A02636454/2022*	2010.1	10	20	40	40	160	320	320	10	20	40	<10	320	80
A/swine/Utah/A02524953/2020	2010.1	10	40	40	40	160	320	640	<10	10	20	10	320	80
A/swine/Indiana/A02635878/2021	2010.2	20	20	20	10	<10	20	40	10	20	20	<10	160	20
rg-A/Cambodia/e826360/2020-like	3C.2a1b.2a.1	<10	<10	<10	<10	<10	10	80	160	80	40	80	160	80
rg-A/Darwin/6/2021-like	3C.2a1b.2a.2	<10	<10	10	<10	<10	20	20	20	40	160	320	40	20
A/HongKong/45/2019	3C.2a1b.1b	<10	nt	nt	<10	nt	nt	nt	nt	nt	nt	nt	1280	160

Reference CVV in red, seasonal vaccine strains in gray, new swine strains in bold, variant in orange. Homologous titers highlighted in gray. *Previously tested in report 2021a; rg is a synthetic HA/NA on PR8 backbone. Human sera were collected in USA with high or low responder relative to A/Hong Kong/45/2019, pools of 2 male and 2 female adults in each.

- The contemporary swine 1990.4.a demonstrated a >8-fold decrease from CVV A/Minnesota/11/2010 x 203 but retained moderate reactivity with adult human sera.
- The contemporary swine 1990.4.b1 does not have a CVV contained within clade and demonstrated a >8-fold decrease from CVV A/Minnesota/11/2010 x 203 but retained reactivity with adult human sera.
- The contemporary swine 2010.1 representative strains had >8-fold loss to CVV IDCDC-RG55C A/Ohio/28/2016-like and had 8-fold loss in cross-reactivity to CVV A/Ohio/13/2017, but 2010.1 retained reactivity with adult human sera.
- The contemporary swine 2010.2 representative strain does not have a CVV contained within and demonstrated reduced titers to human vaccine strains and adult human sera.

Table 20. EU Data: Hemagglutination inhibition of CVV or human seasonal vaccine ferret antisera against contemporary swine H3 strains selected to represent clade consensus.

- > 8 fold reduction
- 8 fold reduction
- 4 fold reduction

	Global Clade	A/Victoria/3/1975	IDCDC-RG55C A/Ohio/28/2016-like CVV	A/Sydney/5/97
A/Victoria/3/1975*	Human seasonal	1280	40	160
IDCDC-RG55C A/Ohio/28/2016-like CVV*	2010.1	160	1280	160
A/Sydney/5/97*	Human seasonal	320	80	2560
A/swine/Italy/308955-3/2021*	1970.1	640	320	320

Reference CVV in red, seasonal vaccine strains in dark red, new swine strains in bold. Homologous titers highlighted in gray. *Previously tested in report 2022b

- The 1970.1 representative demonstrated reactivity with A/Victoria/3/1975, 4-fold decrease to the 2010.1 CVV, and 8-fold decrease to A/Sydney/5/97.

Table 21. Amino acid substitutions between representative swine 1990.4 strains compared to the within-clade CVV (A/Minnesota/11/2010 x 203).

site	A/Minnesota/11/2010	A/swine/North_Carolina/A02245294/2019	A/swine/Iowa/A02750897/2022	A/swine/Kansas/A02750668/2022	annotations
2	K			N	
46	S			T	
48	T			K	
50	R			E	
53	N			S	Site C
57	Q			K	
81	N			D	
82	K			R	
83	E			T	
92	T		A		
96	N	S	S	D	
104	D			E	
107	T			S	
117	N			T	
119	E	K			
124	S	I	I		
131	A	T		N	
135	S			A	
137	Y			F	Site A
138	A	S	S	S	
143	S			A	Site A
144	V			E	Site A
145	N			K	Site A
155	Y			H	Site B
156	N	H	H	S	
158	N			K	
163	E			A	
164	Q			L	
172	D		E	G	
174	F			S	
189	K			A	Site B
192	T			I	
193	N			S	Site B
196	V			T	
201	R			G	Site D
202	V			I	
203	I			T	
207	K	R	R		Site D
216	N			T	
217	I			V	Site D
228	S			G	
275	D			G	Site C
276	E			N	
278	N			E	Site C
289	P	S			
299	K			R	
304	A			P	
312	N			S	
323	V	I	I		
aadiff		9	8	43	

Reference CVV in red, HI swine strains in purple.

Table 22. Amino acid substitutions between representative swine 2010.1 strains compared to the within-clade CVV (A/Ohio/13/2017) and recent human variants.

site	A/Ohio/13/2017	A/swine/Utah/A02524953/2020	A/swine/Iowa/A02636454/2022	A/West_Virginia/26/2022	A/West_Virginia/25/2022	A/West_Virginia/24/2022	A/Michigan/48/2022	A/New_Mexico/19/2022	annotations
25	I			M	M	M	M	M	
31	N		D	D	D	D	D	D	
45	S		N	N	N	N	N	N	
56	Y	H							
62	E		G	G	G	G	G	G	
88	V	I							
92	K	R							
96	N		D	D	D	D	D	D	
106	A		V						
112	V	A							
122	N		K	K	K	K	K	K	Site A
144	S	T							Site A
156	H	Q							
167	T	A							
202	I		T	T	T	T	T	T	
209	N	G							
212	A		T	T	T	T	T	T	
223	V		I	I	I	I	I	I	
238	R		K	K	K	K	K	K	
264	K		R	R	R	R	R	R	
312	N	K							
aadiff		9	11	11	11	11	11	11	

Reference CVV in red, HI swine strains in purple, new variants detection in orange.

Table 23. Amino acid substitutions between a representative 2010.2 strain compared to most similar human seasonal vaccine (A/Stockholm/6/2014) and two human seasonal vaccines used in HI assays (A/Cambodia/e0826360/2020 C.2a1b2a and A/Darwin/6/2021 C.2a1b.2a).

site	A/Stockholm/6/2014	A/Cambodia/e0826360/2020	A/Darwin/6/2021	A/swine/Indiana/A02635878/2021	annotations
3	L	I	I	I	
9	S			G	
31	N			D	
53	D		G		Site C
58	I			V	
62	E	G	G		
83	K	E	E	Q	
92	K	R	R	R	
94	Y	N	N		
106	A			I	
121	N	K	K	K	
128	A	T	T	T	
131	T	K	K		
135	T			I	
138	S	A	A		
144	N	S	S		Site A
156	H		S		
159	S	Y	N	Y	
160	K		I		
164	L		Q		
167	T			I	
171	N		K		
186	G	R	D		Site B
189	K			N	Site B
190	D		N		
192	I			T	
193	F	S	S	S	Site B
195	Y	F	F		
197	Q			R	
198	S	P			
203	T			I	
291	D			N	
aadiff		15	20	18	

Reference vaccine strains in gray, HI swine strain in purple.

Table 24. Amino acid substitutions between a representative swine 1970.1 strain compared to the putative ancestral human seasonal H3 strain (H3 A/Port Chalmers/1/1973); the most similar human seasonal vaccine by amino acid similarity (A/Victoria/3/1975) is included.

site	A/Port Chalmers/1/1973	A/Victoria/3/1975	A/swine/Italy/308955-3/2021	annotations
3	F	L		
6	N		K	
7	D		G	
7+1	-	N		
9	S		N	
31	N		D	
45	S		N	
46	S		F	
48	T		M	
53	N		K	Site C
62	I		A	
67	I		V	
69	A		S	
83	T	K	K	
88	V		I	
92	K		R	
104	D		E	
106	A		T	
112	V		I	
117	T		S	
121	I		T	
124	G		N	
126	T	N	N	
137	N		S	Site A
144	D		N	Site A
145	S		N	Site A
146	G		S	Site A
159	S		N	
160	A	T	T	
163	V		M	
164	L	Q		
171	N		S	
173	N		D	
174	F	S		
189	Q	K	R	Site B
196	V		I	
198	A		T	
201	R	K	K	Site D
202	V		I	
203	T		I	
217	I	V		Site D
242	I		T	
244	V		I	
260	M		I	
261	R		Q	
262	T		I	
267	I		V	
269	R		K	
278	I	S	D	Site C
299	K		R	
307	K		H	
309	V		I	
323	V		I	
aadiff		11	48	

Reference vaccines in gray, HI swine strain in purple.

Summary and Risk Assessment

Global Variant Cases:

During the reporting period (July 1 – December 31, 2022), 14 variant cases were reported and included with the swine analyses:

- USA: H1N2v (1 1A.1.1.3; 1 1A.3.3.2; 3 1B.2.1;), H3N2v (5 2010.1)
- Brazil: H1N1v (1A.3.3.2)
- Netherlands: H1N2v (1 1C.2.2)*
- Spain: H1N1v (1 1C.2.6)*
- Taiwan: H1N2v (1 1C.2.5)*

An additional variant case was detected April 8 2022, and presented by China CDC that was not described in prior OFFLU reports:

- China: H1N1v (1 1C.2.3 – no sequence data)

Europe Swine:

- The contemporary swine 1A.3.3.2 (pdm) with onward transmission in European swine retained variable cross-reactivity to A/California/7/2009.
- There are no within-clade CVVs for 1B lineages from Europe. The swine 1B.1.1 had significant loss in cross-reactivity with A/Chile/1/1983. The contemporary swine 1B.1.2.2 had significant decrease in cross reactivity against both the 1B.2.1 d2 CVV and against the human seasonal reference strain.
- The 1C.2.1 swine strain retained reactivity to the within clade CVV. The 1C.2.2 swine strain retained cross-reactivity with the within clade CVV. The 1C.2.4 swine strains displayed >8-fold reduction to the within clade CVV. The 1C.2.5 swine strain has no within clade CVV but reacted to the 1C.2.4 CVV. The 1C.2.6 swine strains have no within clade CVV and had limited cross-reactivity to CVV in other 1C clades. Variants have been reported in each named H1 1C clade (1C.2.1 – 1C.2.6); within-clade CVVs are available for 1C.2.1 - 1C.2.4. This report period included variants in the 1C.2.5 and the newly identified 1C.2.6 clades; neither has a within-clade CVV, but both are rarely detected in current surveillance activities.
- The representative swine H3.1970.1 demonstrated reactivity with A/Victoria/3/1975, 4-fold decrease to the 2010.1 CVV, and 8-fold decrease to A/Sydney/5/97.

North America Swine:

- The contemporary swine 1A.1.1 (alpha-del) had >8-fold decrease from 1A.1.1 CVV A/Ohio/24/2017 ferret anti-sera and had significant decreases in titer in human sera.
- The 1A.2 swine strain was not significantly detected by any CVV or vaccine anti-sera but reacted with adult human sera.
- The contemporary swine 1A.3.3.2 (pdm) with onward transmission in swine retained cross-reactivity to A/Hawaii/70/2019-like 6B.1A.5a.1 vaccine strain and with adult human sera.
- The contemporary swine 1A.3.3.3 (gamma) clade 1 virus had an 8-fold decrease with the within-clade 1A.3.3.3-clade 1 CVV A/Ohio/09/2015 and 4- to 8-fold reduction in adult human sera. The contemporary swine 1A.3.3.3 (gamma) clade 3 virus had an 8-fold decrease with the 1A.3.3.3-clade 1 CVV A/Ohio/09/2015 but retained reactivity with adult human sera.
- The swine 1A.4 (gamma-2-beta-like) virus had limited detection by any CVV or vaccine anti-sera and 4- to 8-fold decrease with the adult human sera.
- The contemporary swine 1B.2.1 (delta-2) had no loss of titer to the within-clade CVV A/Michigan/383/2018 but limited titers in adult human sera.

- The 1B.2.2.1 A/swine/Wyoming/A02525343/2021 had a >8-fold reduction from the within clade CVV A/Iowa/32/2016 and limited titers in adult human sera.
- The contemporary swine 1B.2.2.2 (delta-1b) does not have a CVV contained within clade and had a > 8-fold decrease from CVV A/Iowa/32/2016 and limited titers in adult human sera.
- The contemporary swine 1990.4.a demonstrated a >8-fold decrease from CVV A/Minnesota/11/2010 x 203 but retained moderate reactivity with adult human sera.
- The contemporary swine 1990.4.b1 does not have a CVV contained within clade and demonstrated a >8-fold decrease from CVV A/Minnesota/11/2010 x 203 but retained reactivity with adult human sera.
- The contemporary swine 2010.1 representative strains had >8-fold loss to CVV IDCDC-RG55C A/Ohio/28/2016-like and had 8-fold loss in cross-reactivity to CVV A/Ohio/13/2017, but retained reactivity with adult human sera.
- The contemporary swine 2010.2 representative strain does not have a CVV contained within and demonstrated reduced titers to human vaccine strains and adult human sera.

Annex 1. Geographic Distribution of swine HA phylogenetic clades by country

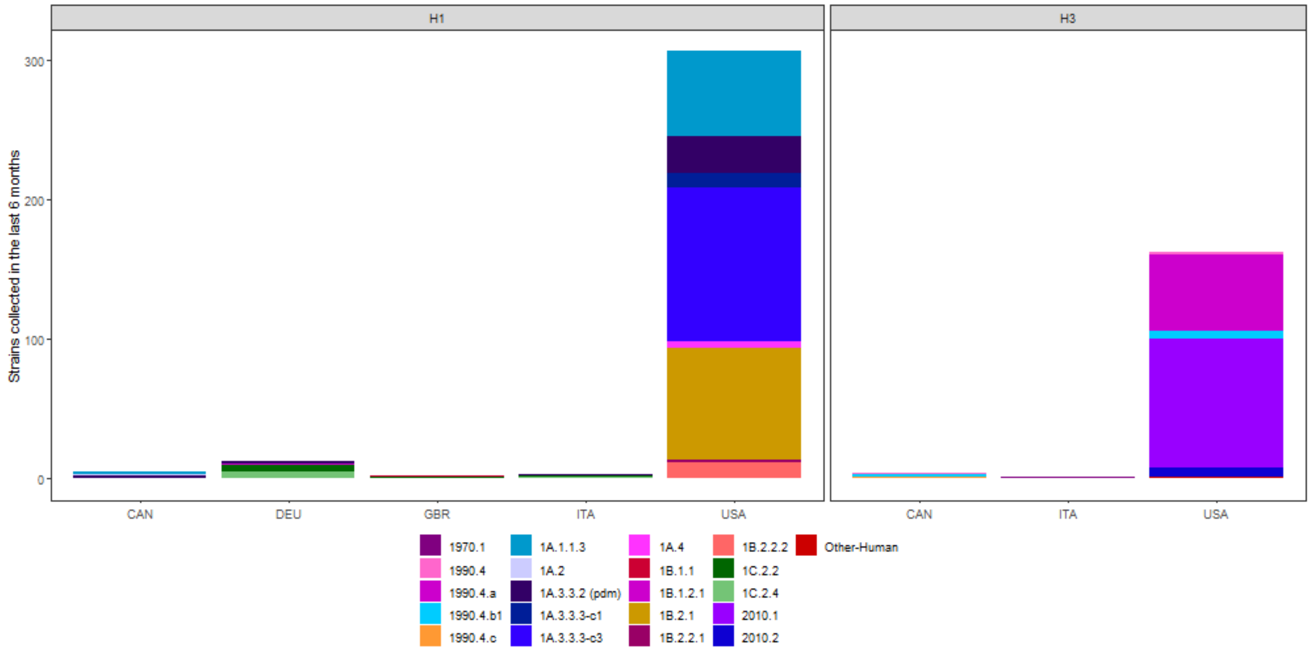


Figure A1. Summary of swine HA genes colored by phylogenetic clade for sequences deposited July 2022 – December 2022 and truncated to those collected within the last 6 months (n=492).

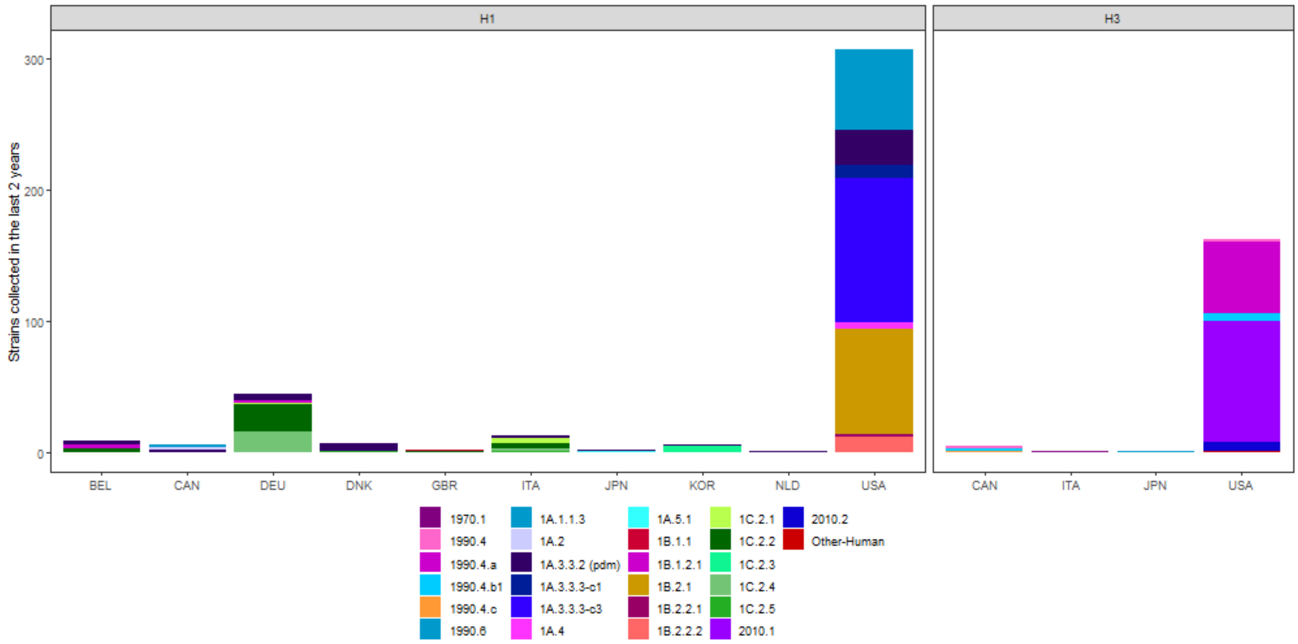


Figure A2. Summary of swine HA genes colored by phylogenetic clade for sequences deposited December 2020 – December 2022 and truncated to those collected within the last 24 months (n= 568).

Table A1a. Summary of swine H1 clades by country collected in the past 6 months and deposited July 2022 – December 2022.

clade	country	count
1A.1.1.3	CAN	2
1A.2	CAN	1
1A.3.3.2	CAN	2
1A.3.3.2-EU	DEU	2
1B.1.2.1	DEU	1
1C.2.2	DEU	5
1C.2.4	DEU	5
1B.1.1	GBR	1
1C.2.2	GBR	1
1A.3.3.2-EU	ITA	1
1C.2.2	ITA	1
1C.2.4	ITA	1
1A.1.1.3	USA	60
1A.3.3.2	USA	26
1A.3.3.3-c1	USA	9
1A.3.3.3-c3	USA	109
1A.4	USA	5
1B.2.1	USA	80
1B.2.2.1	USA	2
1B.2.2.2	USA	12

Table A1b. Summary of swine H1 clades by country collected in the past 24 months and deposited July 2022 – December 2022.

clade	country	count
1A.3.3.2-EU	BEL	3
1B.1.2.1	BEL	3
1C.2.2	BEL	3
1A.1.1.3	CAN	2
1A.2	CAN	2
1A.3.3.2	CAN	2
1A.3.3.2-EU	DEU	5
1B.1.2.1	DEU	2
1C.2.1	DEU	1
1C.2.2	DEU	21
1C.2.4	DEU	16
1A.3.3.2-EU	DNK	6
1C.2.5	DNK	1
1B.1.1	GBR	1
1C.2.2	GBR	1
1A.3.3.2-EU	ITA	4
1B.1.2.2	ITA	1
1C.2.1	ITA	5
1C.2.2	ITA	4
1C.2.4	ITA	3
1C.2.5	ITA	2
1A.3.3.2	JPN	1
1A.5.1	JPN	1
1A.3.3.2	KOR	1
1C.2.3	KOR	5
1A.3.3.2-EU	NLD	1
1A.1.1.3	USA	60
1A.3.3.2	USA	26
1A.3.3.3-c1	USA	9
1A.3.3.3-c3	USA	109
1A.4	USA	5
1B.2.1	USA	80
1B.2.2.1	USA	2
1B.2.2.2	USA	12

Table A2a. Summary of swine H3 clades by country collected in the past 6 months and deposited July 2022 – December 2022.

clade	country	count
1990.4	CAN	1
1990.4.b2	CAN	2
1990.4.c	CAN	1
1970.1	ITA	1
1990.4	USA	2
1990.4.a	USA	53
1990.4.b1	USA	5
1990.4a	USA	1
2010.1	USA	92
2010.2	USA	7
Other-Human-2020	USA	1

Table A2b. Summary of swine H3 clades by country collected in the past 24 months and deposited July 2022 – December 2022.

clade	country	count
1990.4	CAN	2
1990.4.b2	CAN	2
1990.4.c	CAN	1
1970.1	ITA	1
1990.6	JPN	1
1990.4	USA	2
1990.4.a	USA	53
1990.4.b1	USA	5
1990.4a	USA	1
2010.1	USA	92
2010.2	USA	7
Other-Human-2020	USA	1

Annex 2. Phylogenies of swine HA lineages with tree backbone annotated by inferred amino acid mutations.

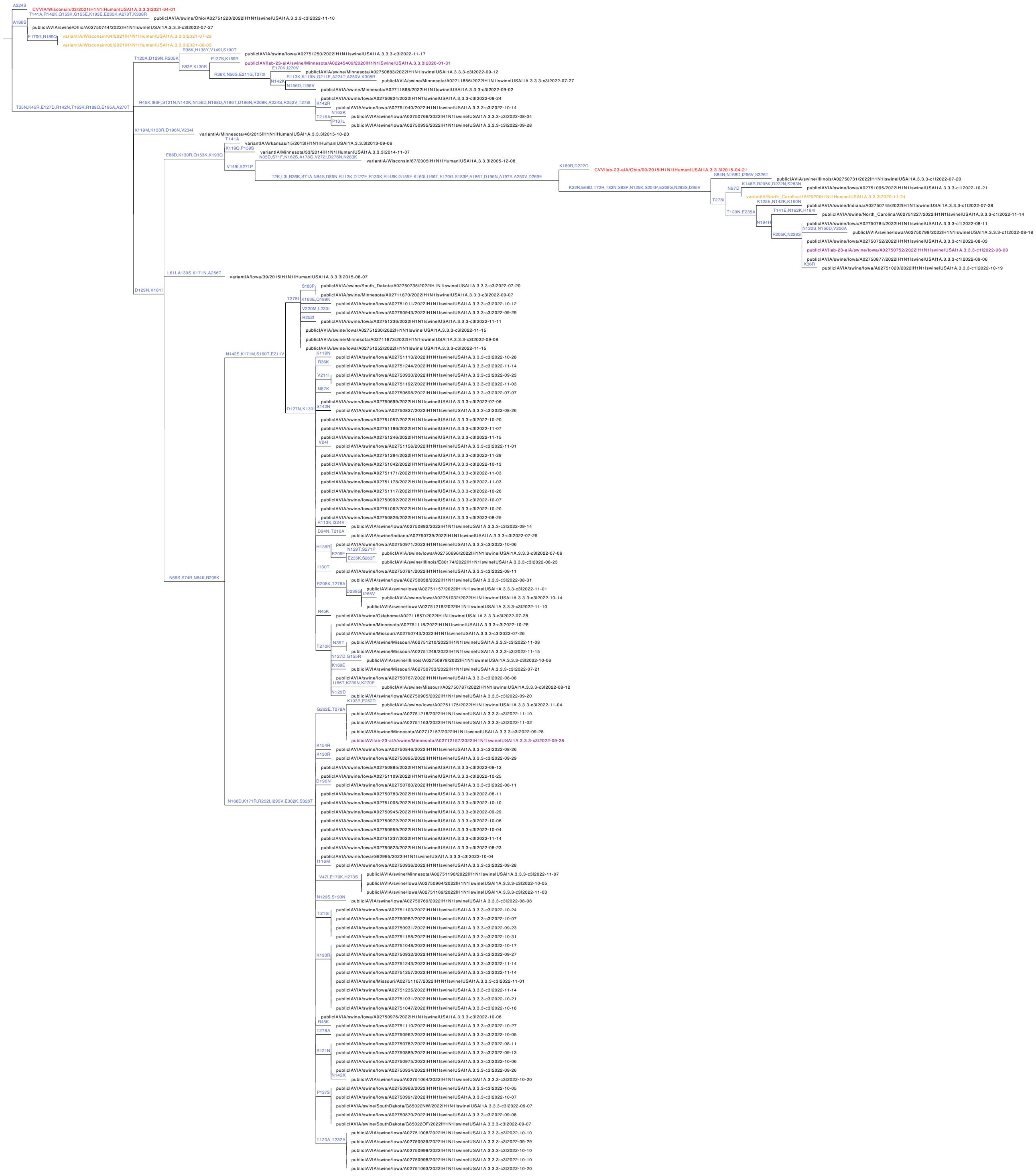


Figure A3. A phylogeny of the **1A.3.3.3** clade displaying sequences deposited July 1, 2022 - December 31, 2022 and collected in 2022 (n=121) and 10 reference genes. The clade is rooted relative to the most recent in-clade CVV (A/Wisconsin/03/2021) and all branches are annotated by the respective amino acid mutations in the HA1 region. The strains are colored in consistence with Figure 7.

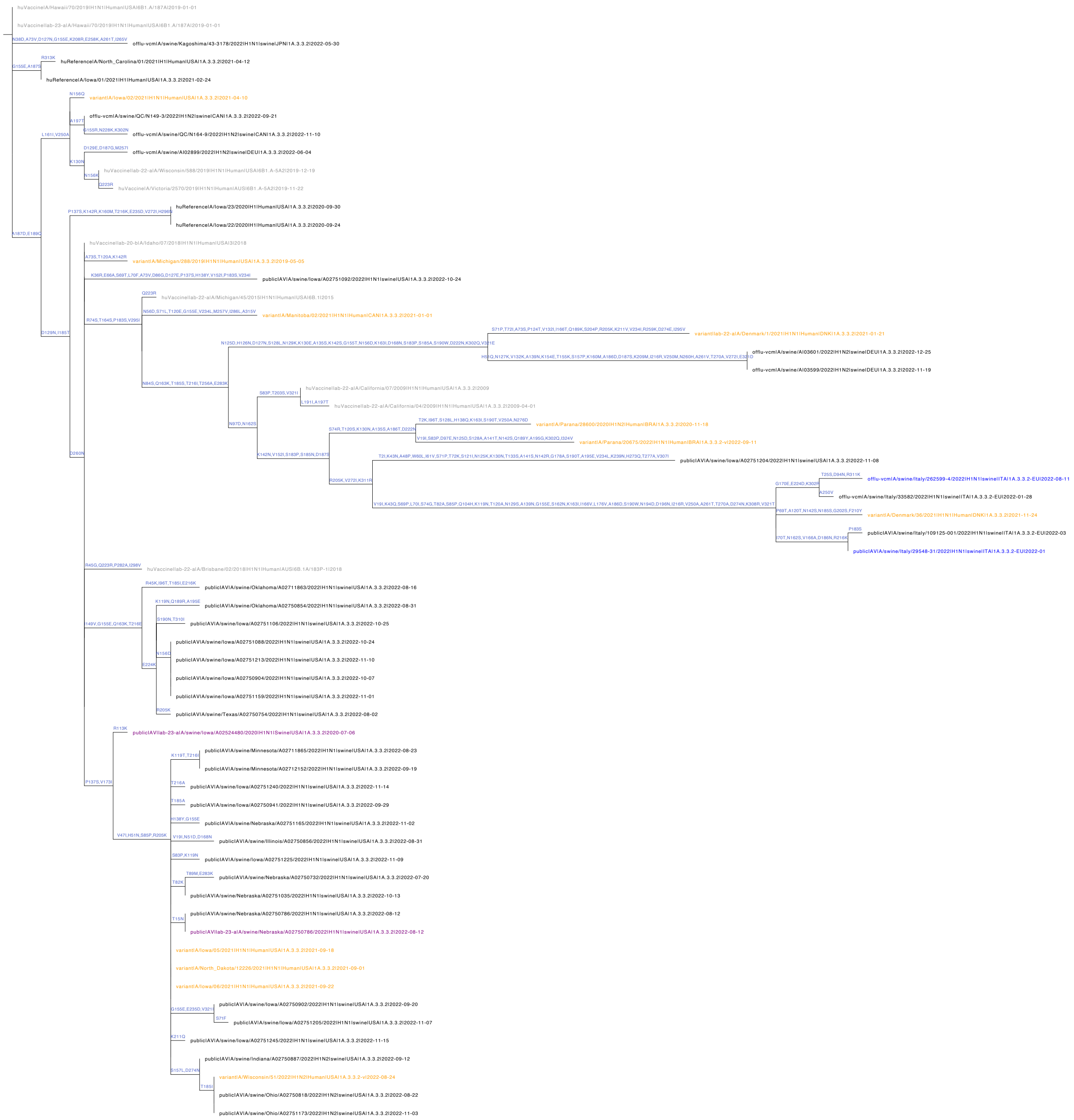


Figure A4. A phylogeny of the **1A.3.3.2 (pdm)** clade displaying n=38 sequences deposited July 1, 2022 - December 31, 2022 and collected in 2022, and n=24 reference genes. The clade is rooted relative to the most recent human vaccine strain (A/Hawaii/70/2019) and all branches are annotated by the respective amino acid mutations in the HA1 region. The strains are colored in consistence with Figure 7.

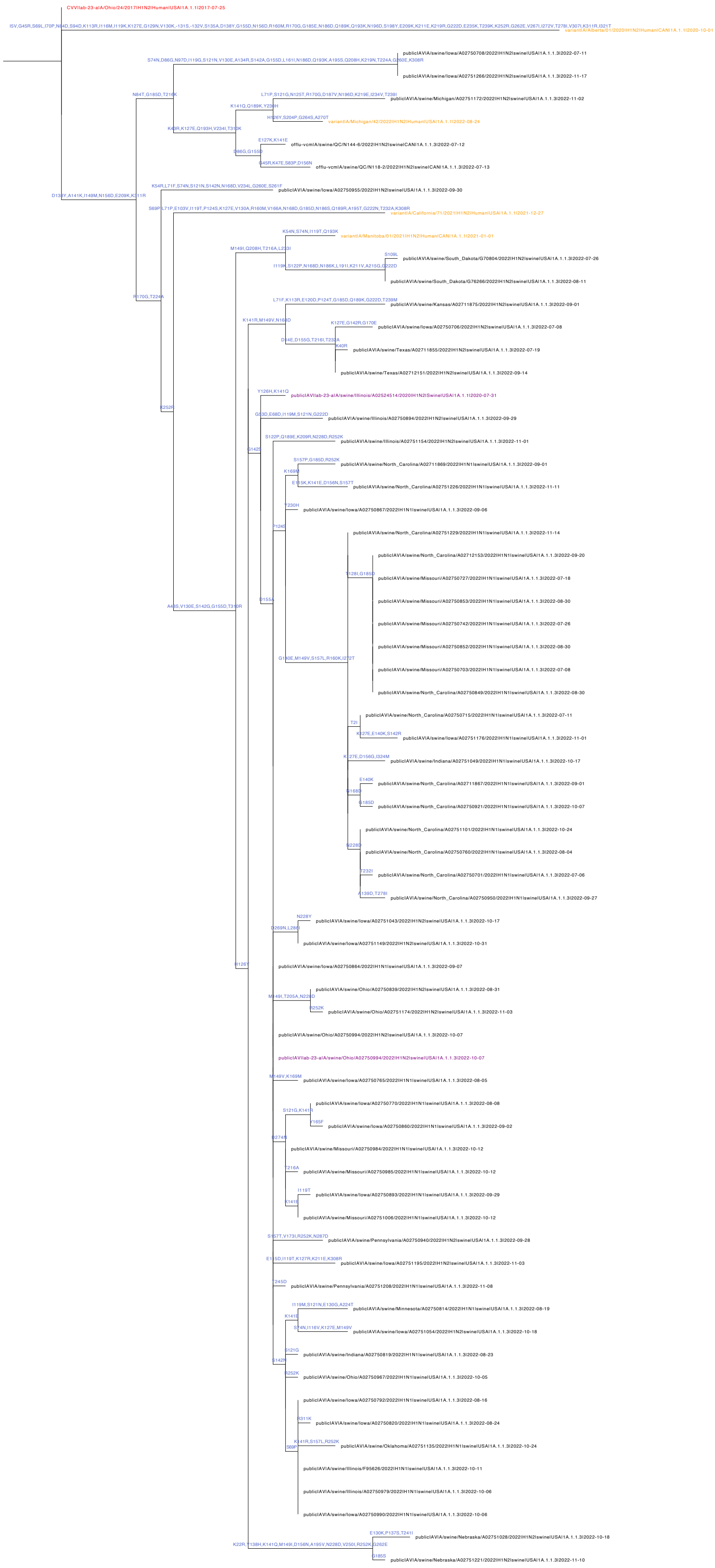


Figure A5. A phylogeny of the **1A.1.1.3** clade displaying n=64 sequences deposited July 1, 2022 - December 31, 2022 and collected in 2022, and n=5 reference genes. The clade is rooted relative to the most recent in-clade CVV (A/Ohio/24/2017) and all branches are annotated by the respective amino acid mutations in the HA1 region. The strains are colored in consistence with Figure 7.

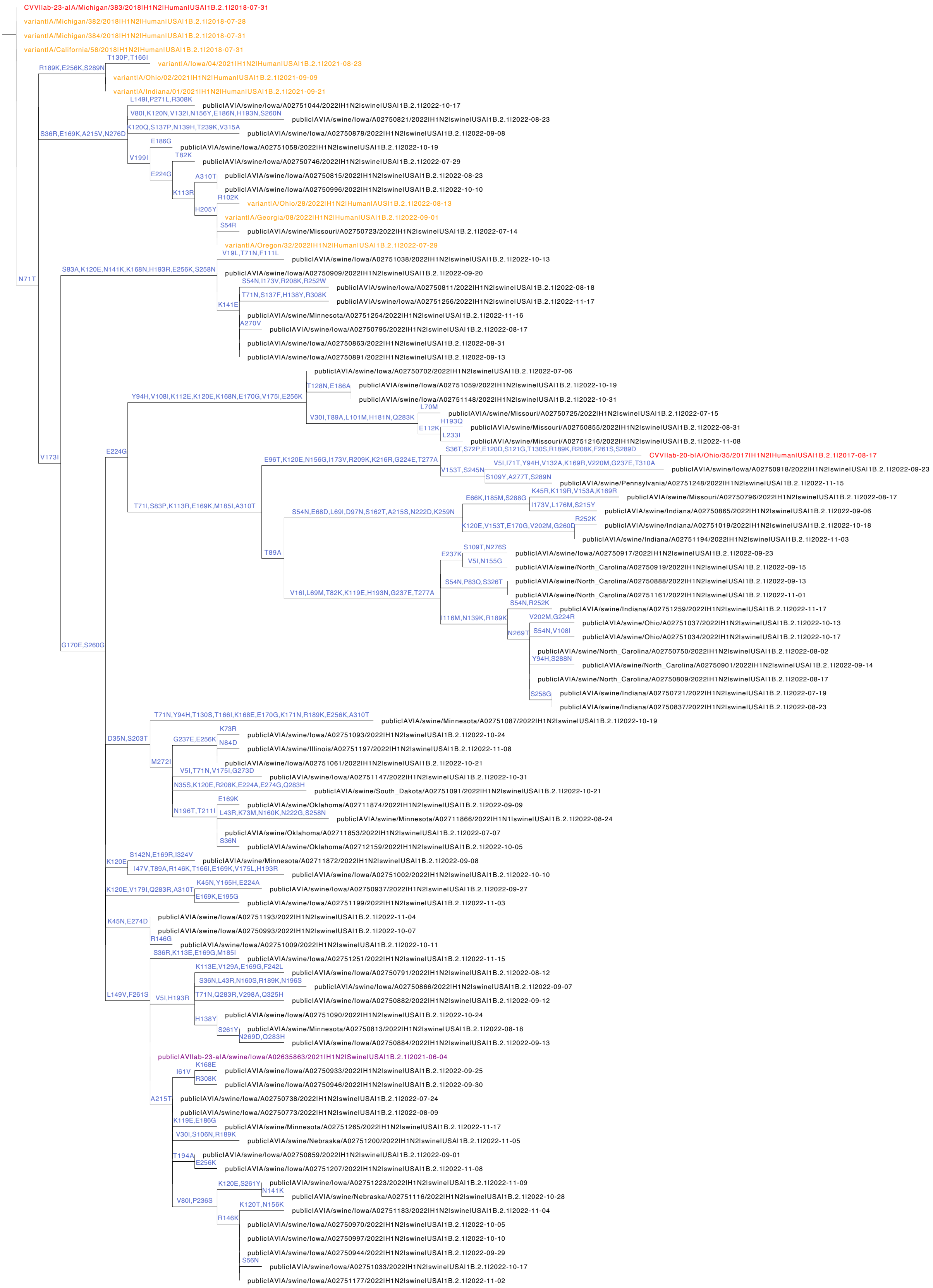


Figure A6. A phylogeny of the **1B.2.1** clade displaying n=81 sequences deposited July 1, 2022 - December 31, 2022 and collected in 2022, and n=11 reference genes. The clade is rooted relative to the most recent in-clade CVV (A/Michigan/383/2018) and all branches are annotated by the respective amino acid mutations in the HA1 region. The strains are colored in consistence with Figure 8.

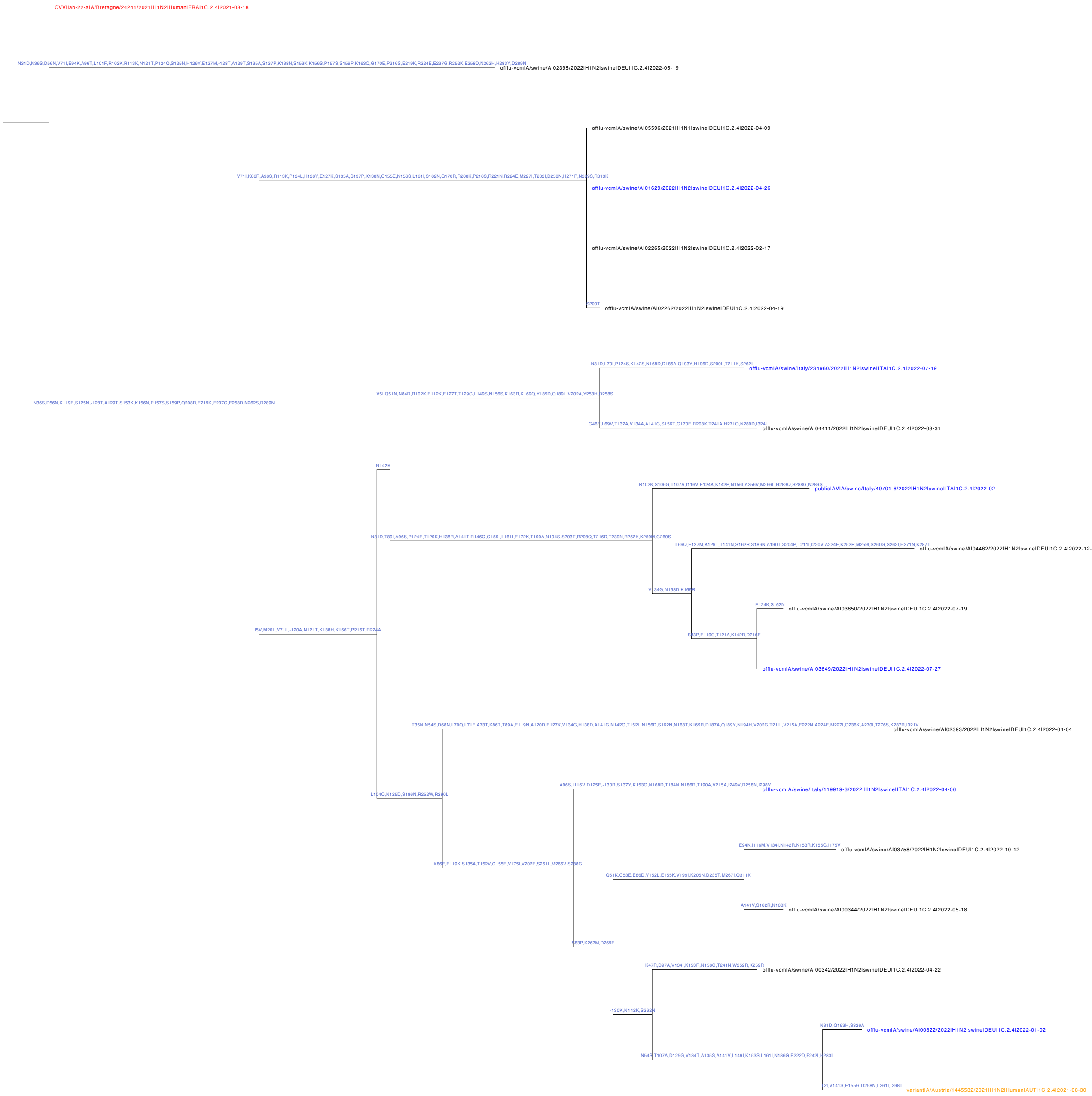


Figure A7. A phylogeny of the **1C.2.4** clade displaying n=17 sequences deposited July 1, 2022 - December 31, 2022 and collected in 2022, and n=2 reference genes. The clade is rooted relative to the closest CVV (A/Britagne/24241/2021) and all branches are annotated by the respective amino acid mutations in the HA1 region. The strains are colored in consistence with Figure 9.

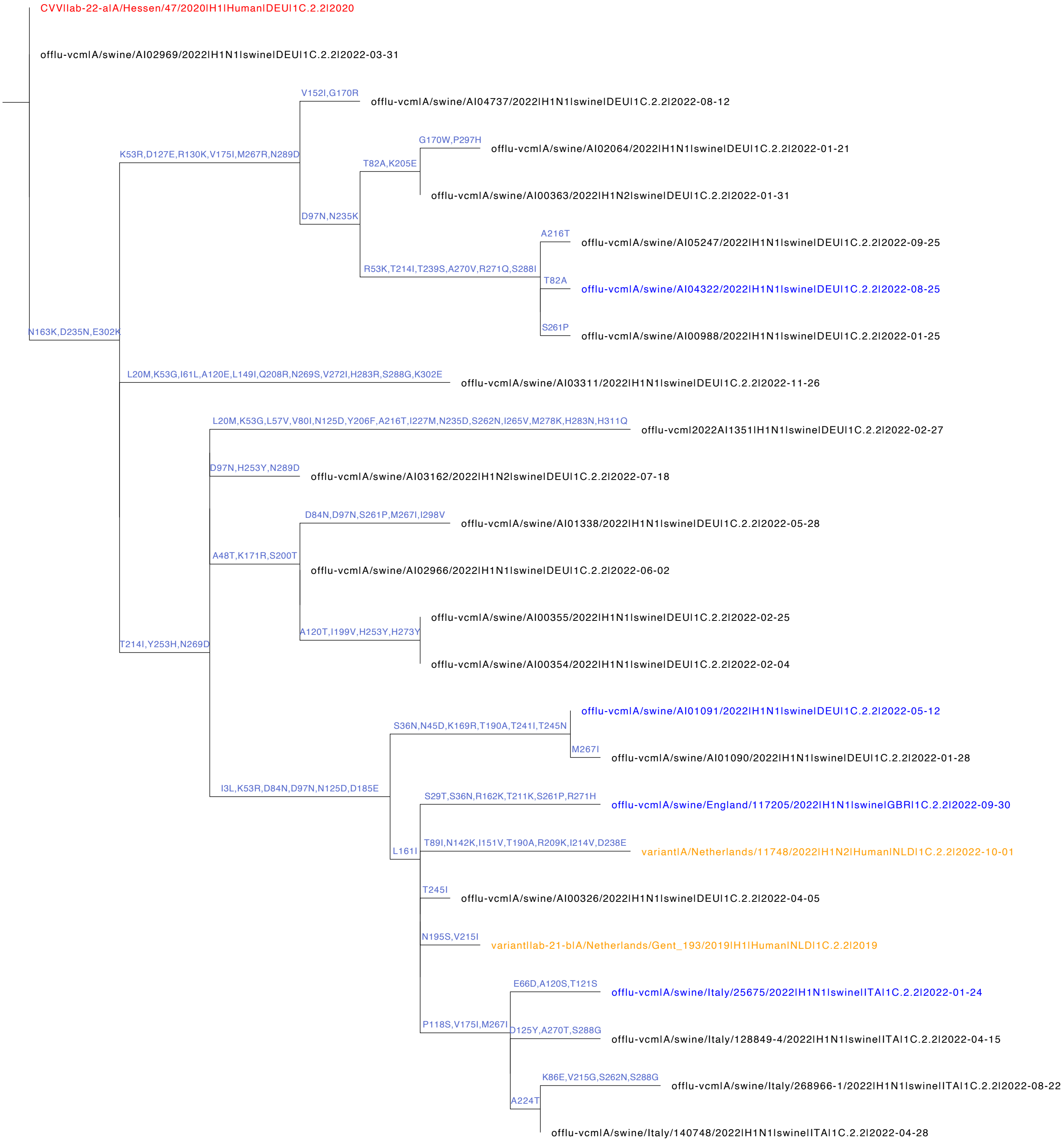


Figure A8. A phylogeny of the **1C.2.2** clade displaying n=21 sequences deposited July 1, 2022 - December 31, 2022 and collected in 2022, and n=3 reference genes. The clade is rooted relative to the closest CVV (A/Hessen/47/2020) and all branches are annotated by the respective amino acid mutations in the HA1 region. The strains are colored in consistence with Figure 9.

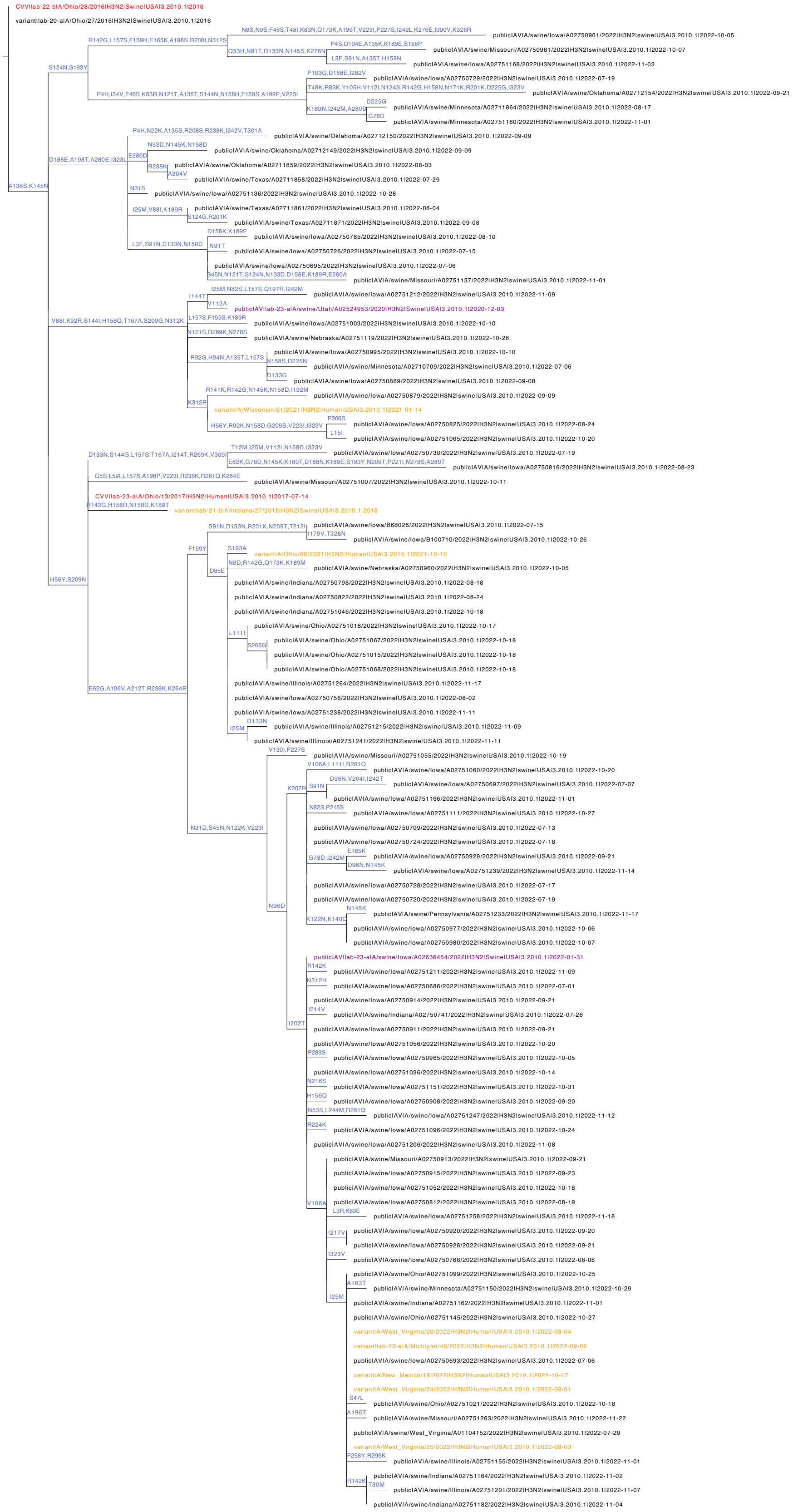


Figure A9. A phylogeny of the **3.2010.1** clade displaying n=94 sequences deposited July 1, 2022 - December 31, 2022 and collected in 2022, and n=11 reference genes. The clade is rooted relative to the most representative in-clade CVV (A/Ohio/28/2016) and all branches are annotated by the respective amino acid mutations in the HA1 region. The strains are colored in consistence with Figure 10.

Figure A10. A phylogeny of the **3.1990.4.a** clade displaying n=55 swine sequences deposited July 1, 2022 - December 31, 2022 and collected in 2022, and n=3 reference genes. The clade is rooted relative to the most representative in-clade CVV (A/Minnesota/11/2010) and all branches are annotated by the respective amino acid mutations in the HA1 region. The strains are colored in consistence with Figure 10.