Update on Zoonotic Infections with Variant Influenza A Viruses in the USA

Todd Davis
Zoonotic Virus Team
Virology, Surveillance and Diagnosis Branch
Influenza Division
CDC, Atlanta

OFFLU Swine Influenza Virus Surveillance Network

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Reporting Requirements for Novel Influenza A Infections in Humans

- In 2007, novel influenza A infections nationally reportable to the National Notifiable Diseases Surveillance System
- Novel influenza A viruses = those that are different from currently circulating human H1 and H3 viruses
- Includes those that cannot be subtyped using standard methods and reagents

Inter-Agency Agreement between CDC and USDA

Collaboration between the Influenza Division and USDA, Animal and Plant Health Inspection Service (APHIS)
National Veterinary Services Laboratory (NVSL).
Development of a National Swine Influenza Virus (SIV) Surveillance Program

Rapidly detect changes in swine influenza virus to increase the knowledge of the Impact of SIV changes on swine health

- Risk assessment
  - identify swine influenza viruses that may pose a threat to human health (ie H2N3, H3N1)
  - co-ordination of surveillance during human outbreaks
- develop improved human biosafety practices to minimize transmission
- Share viruses/reagents

Use of viruses/data from swine influenza surveillance

- Mouse and ferret pathotyping
- Flu diagnostic assays
- Antiviral resistance testing
- Antigenic comparisons
- Pre-pandemic Vaccine Development
- Human population immunity

Provide diagnostic, epidemiologic, and experimental data regarding SIV infection to swine stakeholders
develop new diagnostic reagents for swine
provide material for vaccine updates
improve biosecurity practices to minimize transmission.

Evaluate mutations and how they affect flu diagnostic assays

Current FDA approved CDC Flu rRT-PCR Dx Panel rely on real-time RT-PCR primers and probes to the following gene targets

Influenza A - M gene
Influenza B – NS gene
Human H3 – HA
Human H1pdm – HA
Influenza A/pdm09 – NP gene

RUO - swH3 – HA
RUO – swH1 – HA

Testing Algorithms with the current CDC Flu rRT-PCR Dx Panel identifies H3v and H1v human influenza infections.

Surveillance for mutations in the primer and probe regions must be continually monitored

Antiviral Susceptibility of variant viruses

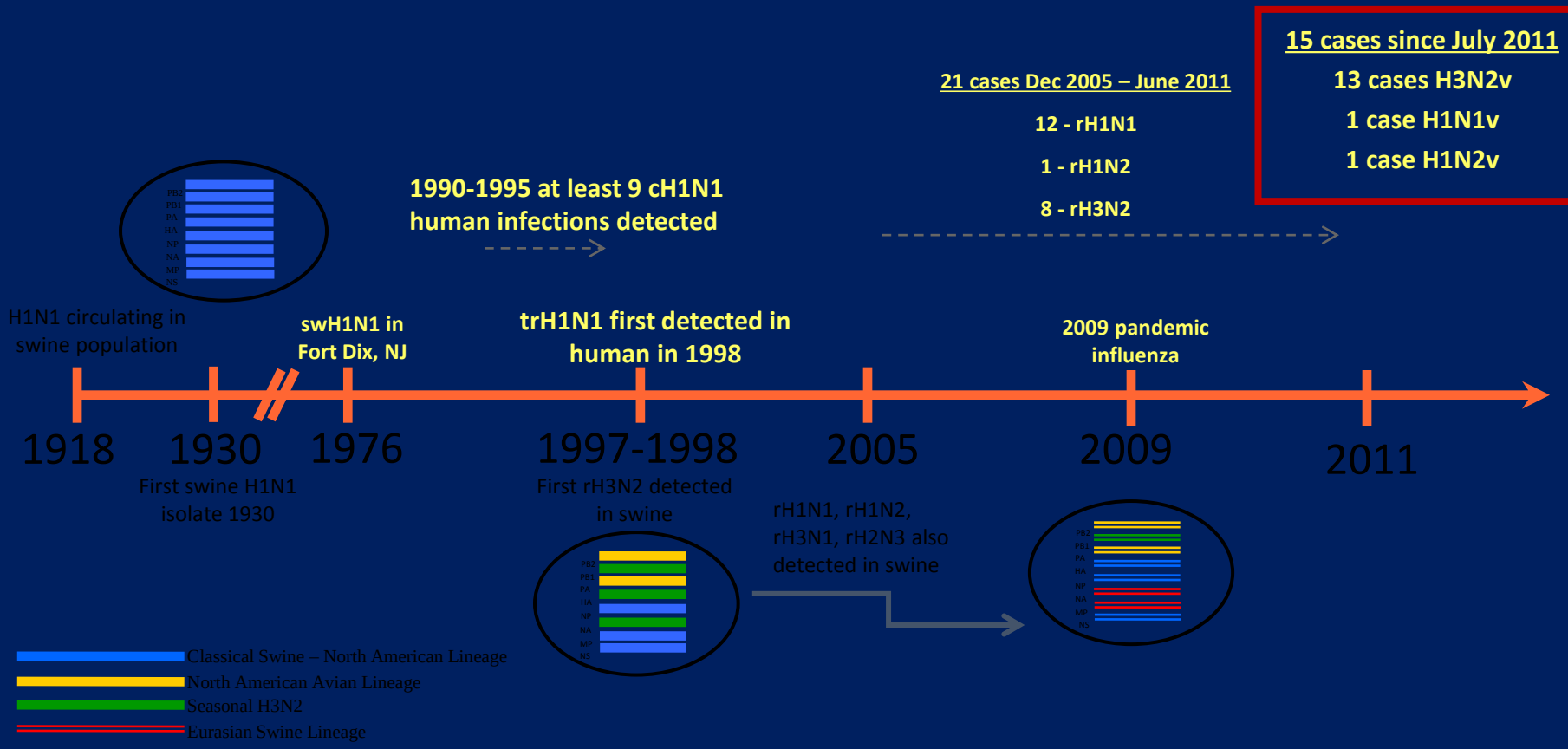
- All H3N2v and H1N1v viruses evaluated are resistant to the amantadine class of drugs (amantadine, rimantadine).
- CDC has deployed antiviral susceptibility testing at several public health departments and at CDC labs.
- The pyrosequencing test used for human H3N2 and H1N1 viruses is suitable for testing variant viruses as well.
- All H3N2v and H1N1v viruses evaluated so fare appear to be susceptible to the commercially available neuraminidase inhibitors oseltamivir (Tamiflu®) and zanamivir (Relenza®).

Antigenic comparisons against current human prototype variant vaccines

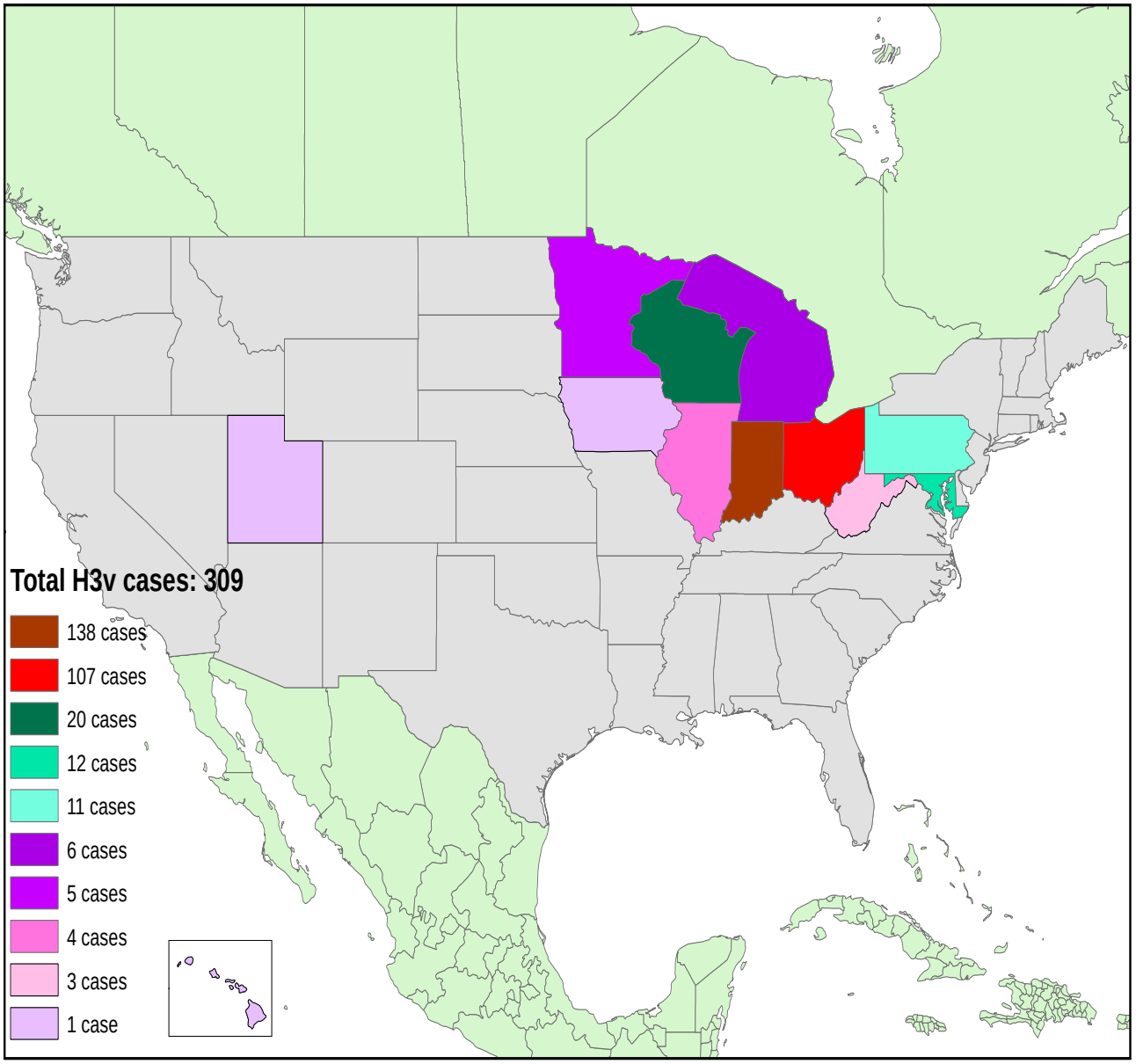
	REFERENCE FERRET ANTISERA		
	Seasonal H3N2	H3N2v	
REFERENCE ANTIGENS	PE/16	KS/13	MN/11
SEASONAL H3N2			
A/PERTH/16/2009	640	5	40
H3N2v			
A/KANSAS/13/2009	5	640	40
A/MINNESOTA/11/2010	5	20	640
A/WEST VIRGINIA/06/2011	5	40	640
A/INDIANA/07/2012	5	40	1280
A/MICHIGAN/16/2012	5	20	1280
A/OHIO/69/2012	5	40	1280
A/OHIO/05/2013	5	40	640
A/INDIANA/04/2013	5	40	160

- All H3N2v viruses tested are antigenically similar to the H3N2v candidate vaccine A/Minnesota/11/2010 but antigenically distinct from seasonal H3N2 viruses. Antigenic differences in H3N2v must be continually monitored for vaccine match.

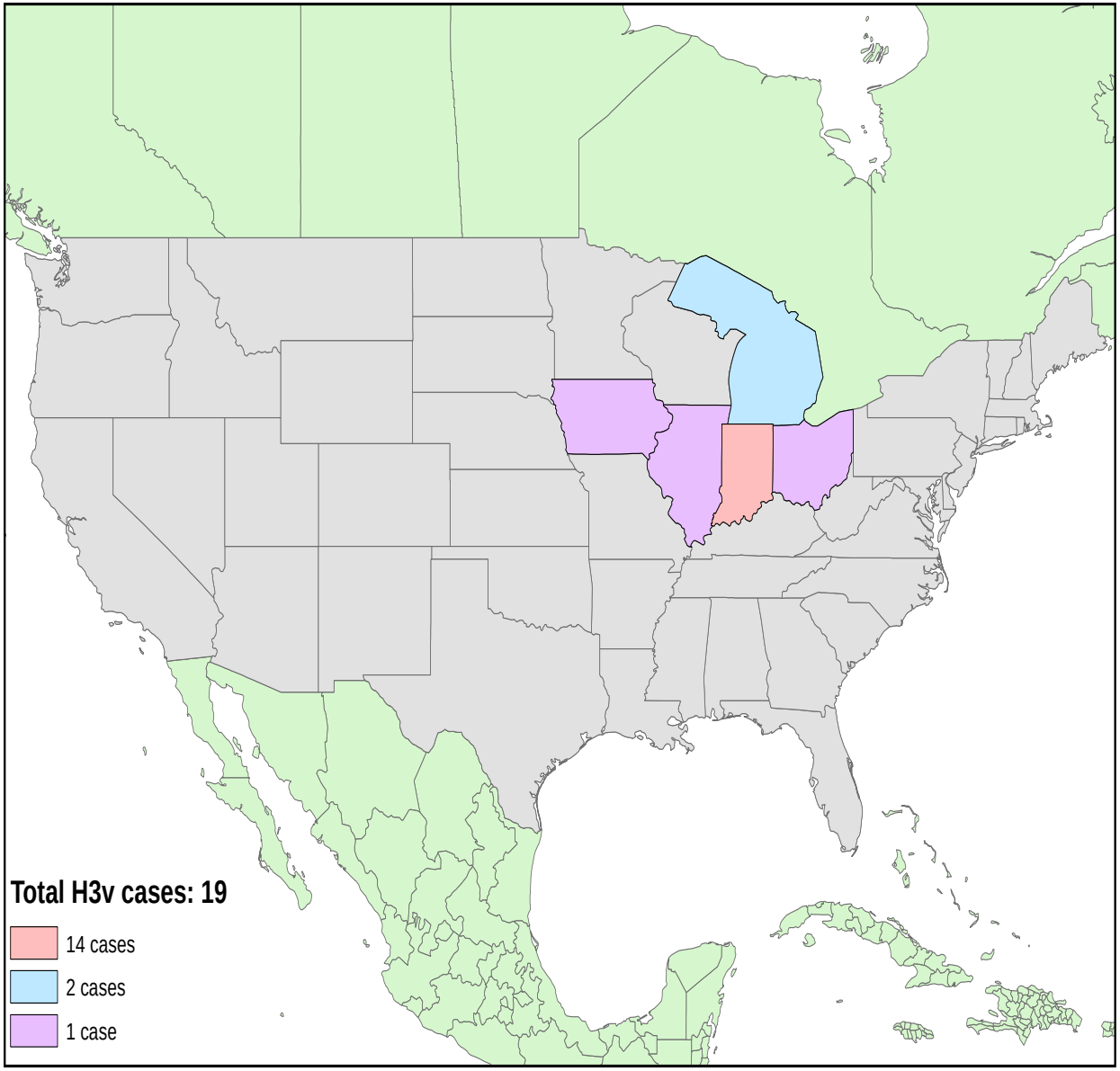
Summary of Swine Influenza virus circulation in pigs and detection of human infections



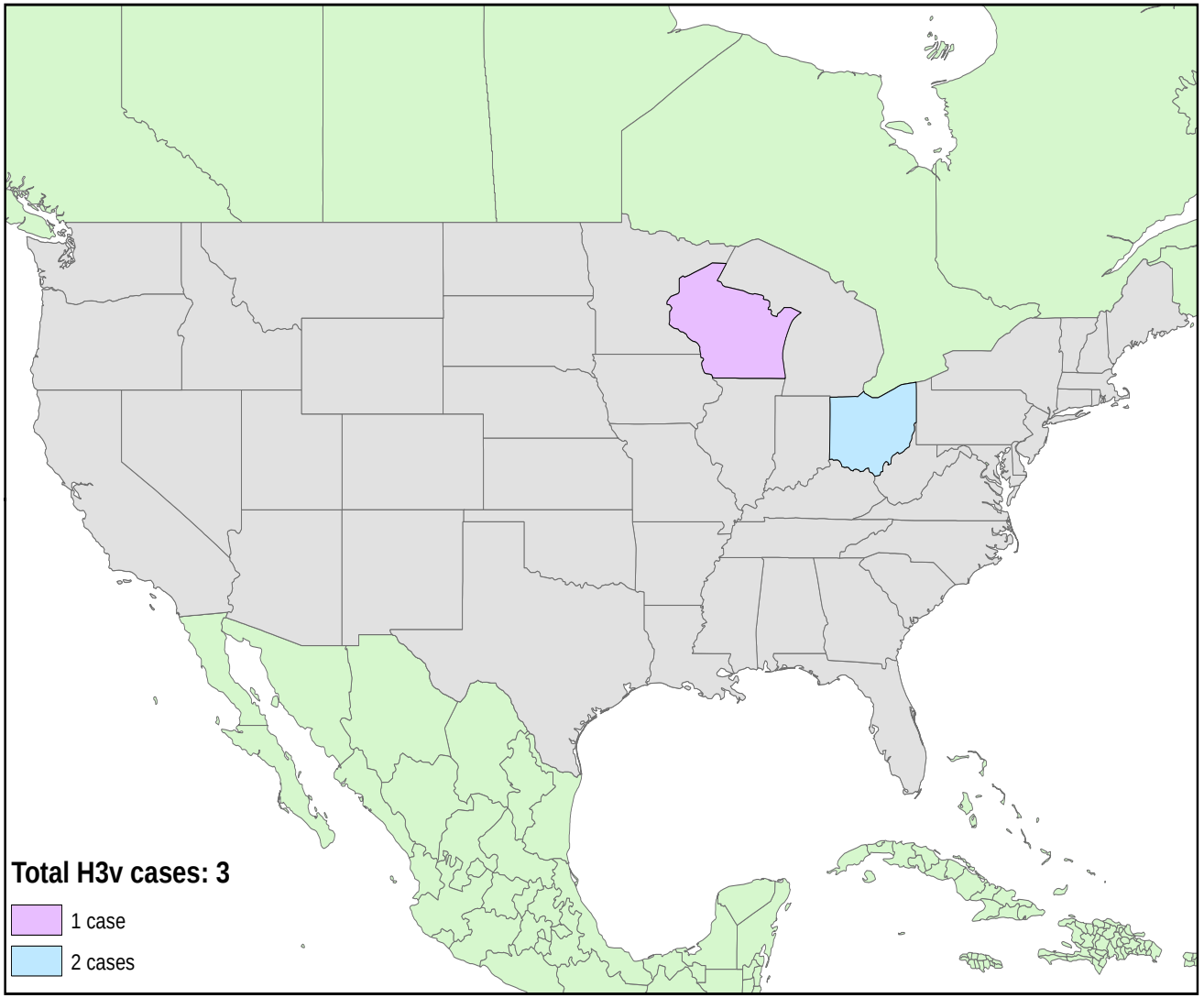
H3N2v 2012


Total H3v cases: 309
138 cases
107 cases
20 cases
12 cases
11 cases
6 cases
5 cases
4 cases
3 cases
1 case

H3N2v 2013



H3N2v 2014



Influenza A(H3N2)v activity in 2015

Two cases of A(H3N2)v were identified in the United States

- Direct swine contact was reported in both instances.

- One patient from Michigan developed illness in June and recovered following oseltamivir treatment.

- In July, an immunocompromised person from Minnesota developed an acute respiratory illness and tested positive for A(H3N2)v.

- Virus isolates from each patient belonged to separate phylogenetic groups of the A(H3N2)v haemagglutinin tree.

Genome Comparisons of H3N2v 2005-2015

Classical Swine – North American lineage

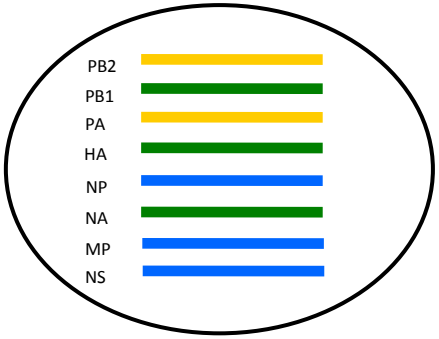
Avian – North American lineage

Seasonal H3N2

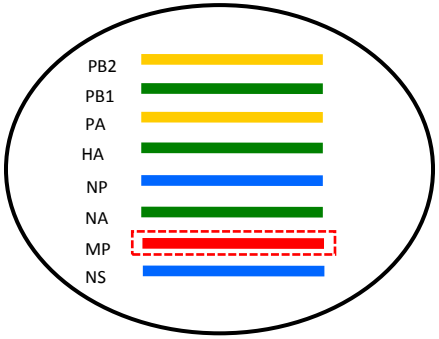
Eurasian swine lineage (from H1N1 pdm09 virus)

Gene derived from H1N1 pdm09 virus

2005-2010

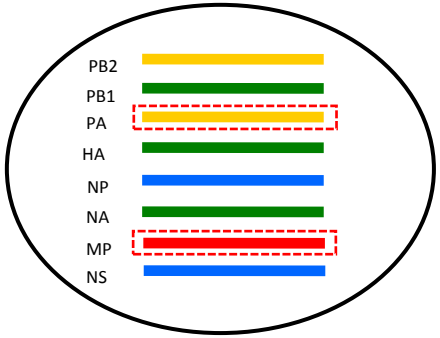


Majority of 2011-2012 (n>300) and 2013 from Indiana (n=13)

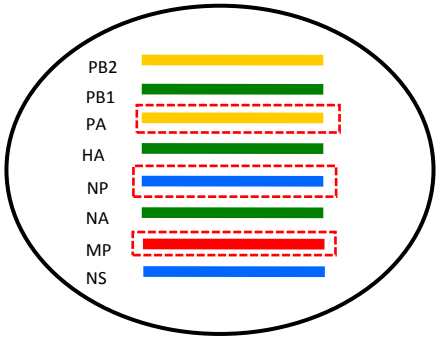


A/Minnesota/38/2015
A/Michigan/39/2015

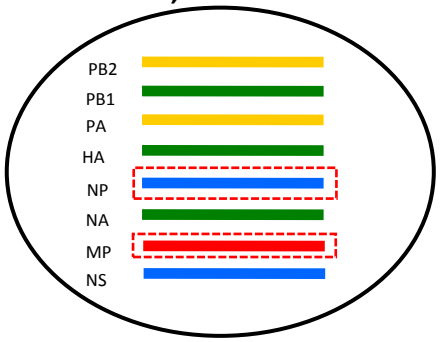
2013 (n=5)
Ohio, Illinois, Indiana, Michigan



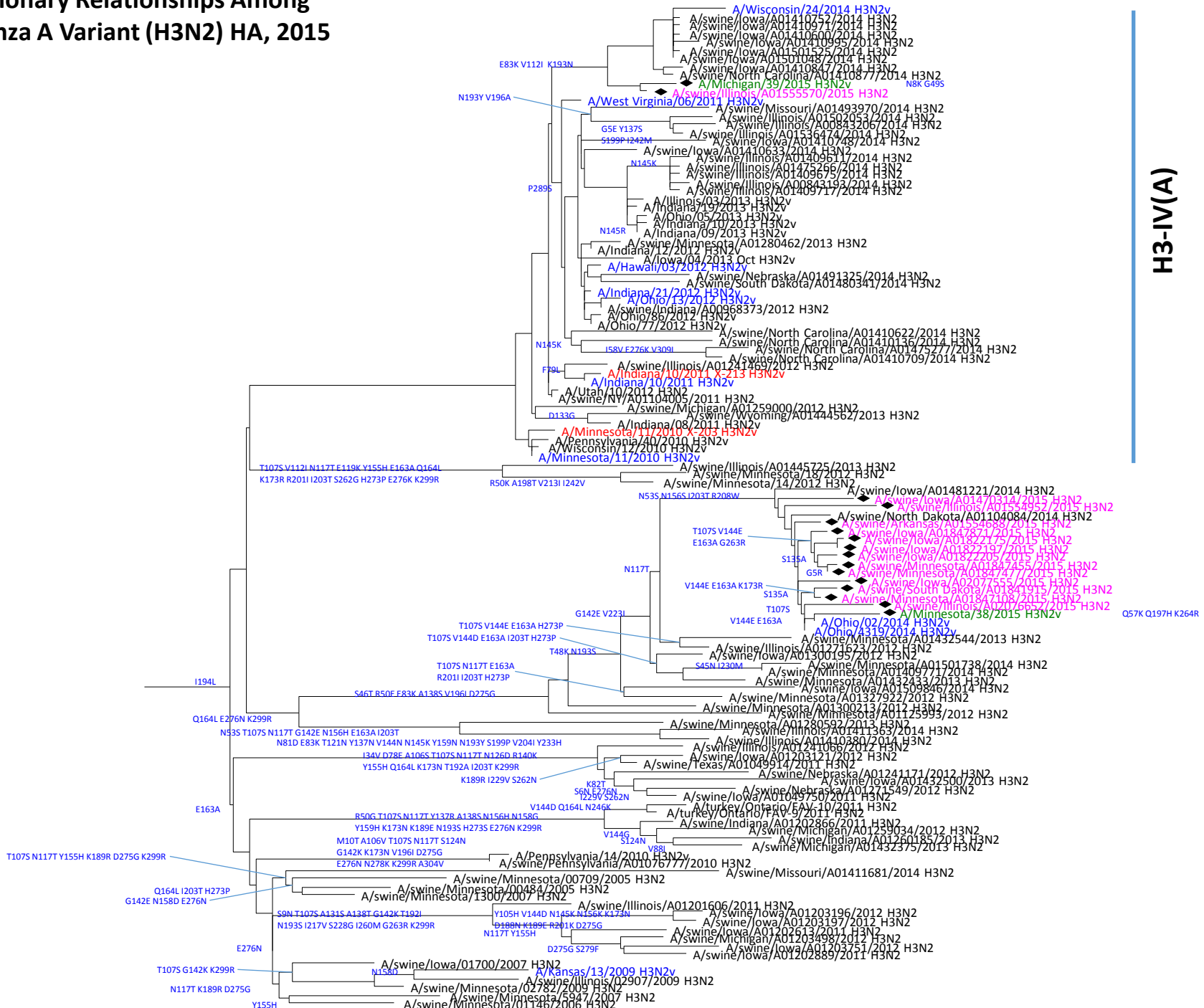
2013 (n=1)
Iowa



2014 (n=3)
Ohio, Wisconsin



Evolutionary Relationships Among Influenza A Variant (H3N2) HA, 2015



Status of A(H3N2)v candidate vaccine virus development

Candidate vaccine viruses	Type	Institution
A/Minnesota/11/2010 (NYMC X-203)	Conventional reassortant	CDC
A/Indiana/10/2011 (NYMC X-213)	Conventional reassortant	CDC

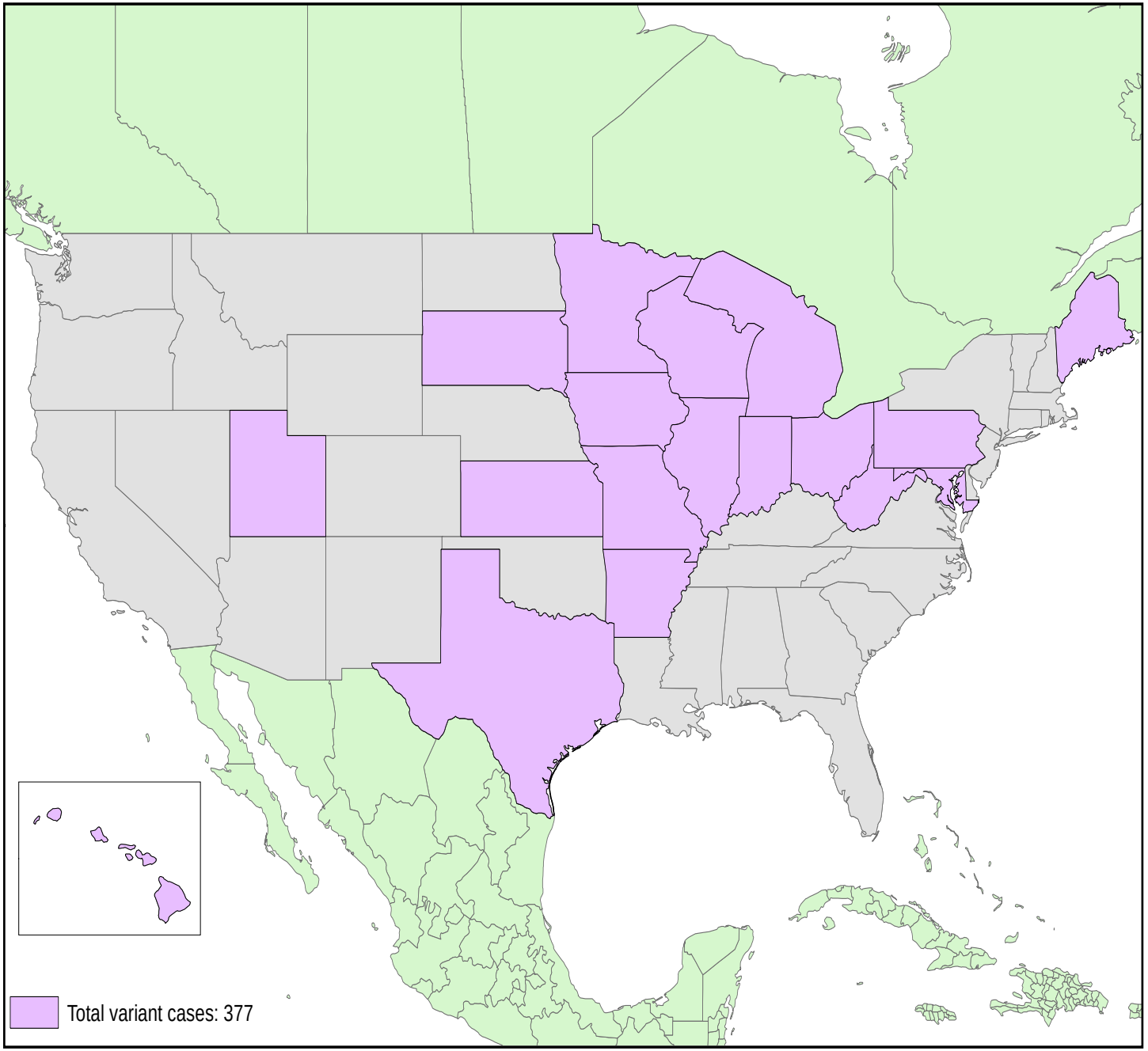
HEMAGGLUTINATION INHIBITION REACTIONS OF INFLUENZA H3N2v VIRUSES

			IV			IV-A					IV-B		3C.3a	
			2009-185	2012-018	2011-030	2011-060	2015-016	2012-174	2012-183	2013-003	2015-013	2015-012	2015-043	Human Pool - 2013/14 vaccinees*
	REFERENCE ANTIGENS	Group	KS/13	IN/10	MN/11	MN/11 X-203	WI/24	HI/03	OH/13	IN/21	OH/4319	OH/2	SWITZ	
1	A/KANSAS/13/2009	IV	5120	160	160	160	80	320	320	1280	20	320	10	160
2	A/INDIANA/10/2011	IV-A	320	2560	2560	1280	2560	5120	5120	1280	640	640	10	160
4	A/MINNESOTA/11/2010	IV-A	160	640	2560	1280	1260	5120	1280	2560	320	640	<	160
5	A/MINNESOTA/11/2010 X-203	IV-A	160	640	1280	5120	640	640	640	320	320	160	20	80
6	A/WISCONSIN/24/2014	IV-A	160	1280	1280	1280	1280	5120	5120	1280	640	640	10	160
7	A/HAWAII/03/2012	IV-A	640	2560	2560	1280	5120	5120	5120	1280	640	1280	<	320
8	A/OHIO/13/2012	IV-A	320	1280	2560	1280	2560	5120	5120	2560	640	640	<	80
9	A/INDIANA/21/2012	IV-A	80	640	640	640	640	1280	2560	1280	80	160	<	160
10	A/OHIO/4319/2014	IV-B	160	2560	640	320	1280	1280	1280	1280	5120	5120	10	160
11	A/OHIO/2/2014	IV-B	320	2560	1280	640	2560	2560	1280	1280	5120	5120	40	320
12	A/SWITZERLAND/9715293/2013	3C.3a	<	40	80	<	20	1280	160	320	20	80	1280	80
	TEST ANTIGENS													
13	A/MINNESOTA/38/2015	IV-B	320	2560	1280	640	2560	2560	1280	1280	5120	5120	40	160
14	A/MICHIGAN/39/2015	IV-A	320	1280	2560	320	1280	5120	5120	1280	320	640	<	80

Indicates comparison to candidate vaccine virus

* Post-vaccine immune serum pool from adult (19-49 yrs) vaccinees

Total variant virus cases since 2005



Influenza A(H1N1)v and A(H1N2)v activity in 2015

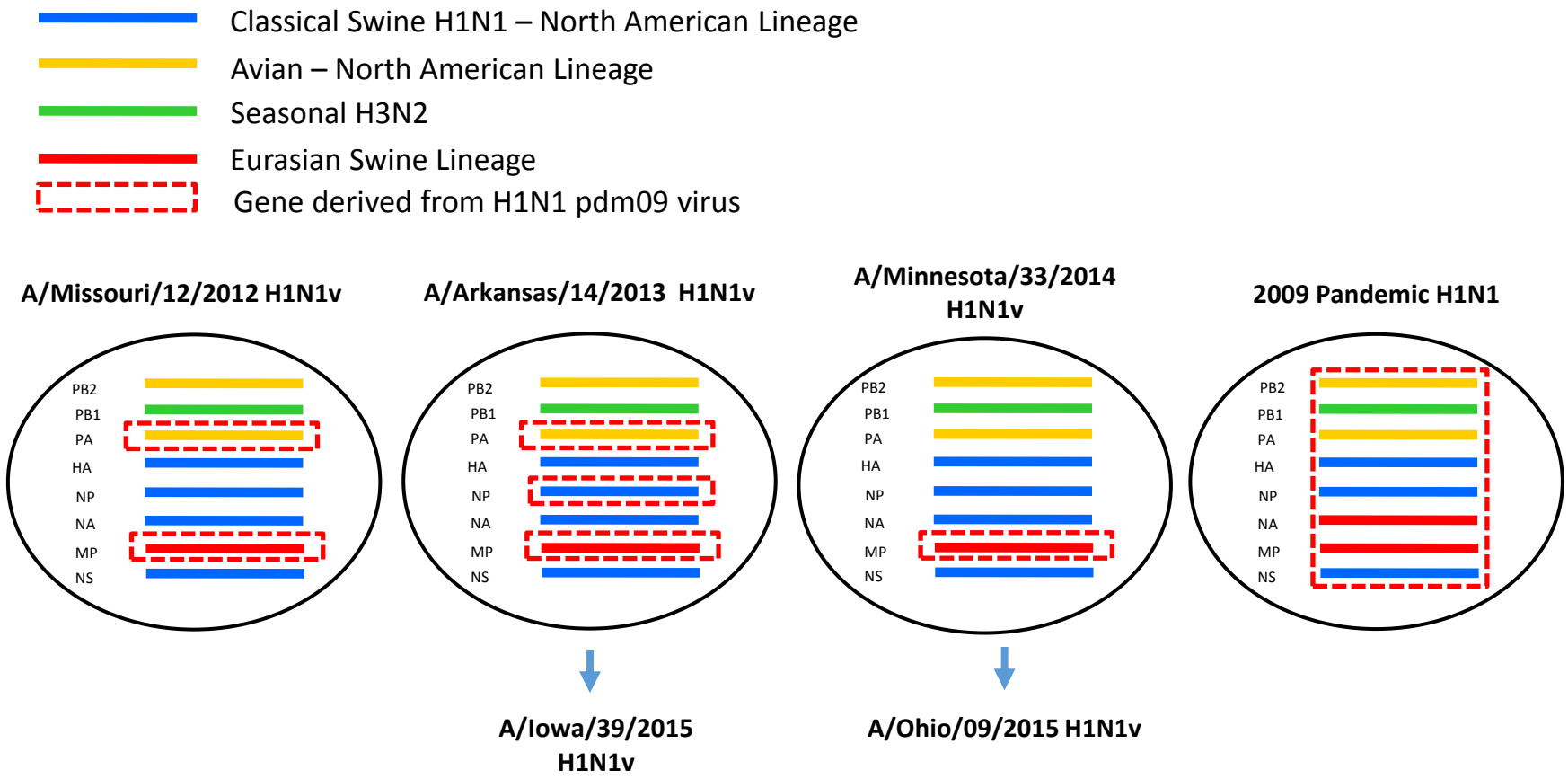
Two cases of A(H1N1)v were identified in the United States

- A fatal case was detected in Ohio during April in a person with potential occupational exposure to swine.

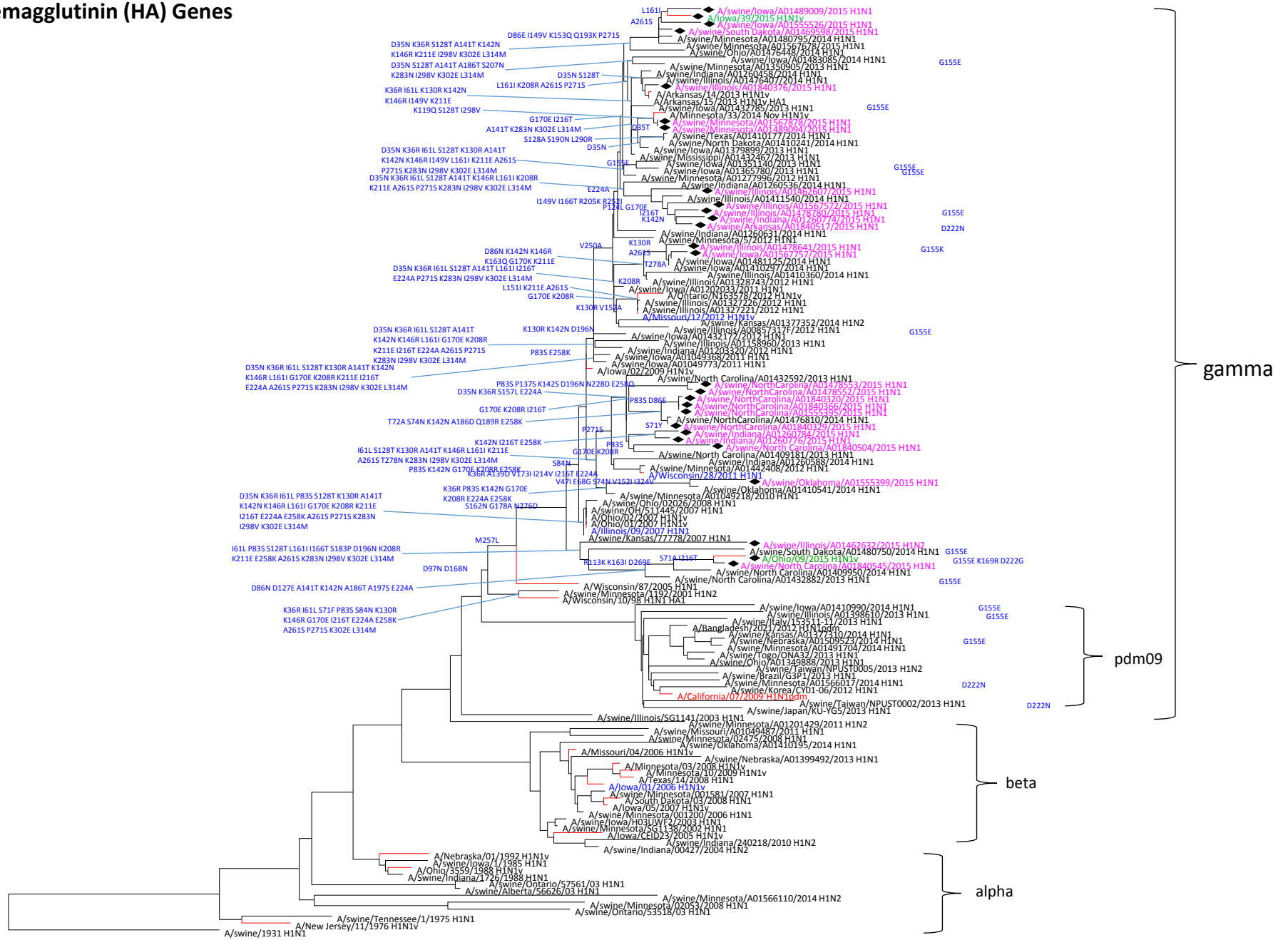
- second severe case in Iowa was hospitalized in August. Direct contact with swine was reported.

- The HA genes of both viruses belonged to the classical swine gamma lineage but were genetically distant to the A(H1N1)pdm09 vaccine virus, A/California/7/2009

Genome Comparisons of H1N1v Viruses



Evolutionary Relationships Among Influenza A Variant (H1) Hemagglutinin (HA) Genes



HEMAGGLUTINATION INHIBITION REACTIONS OF INFLUENZA A(H1N1)v

			REFERENCE ANTISERA					
						New	New	
			β	γ	γ	γ	γ	
		pdm H1	H1N1v	H1N1v	H1N1v	H1N1v	H1N1v	Human pool - 2013/14
REFERENCE ANTIGEN	Lineage	CA/7	IA/1	WI/28	MO/12	MN/33	OH/09	vaccinees *
1 A/CALIFORNIA/7/2009	pdmH1	5120	2560	5120	2560	2560	160	1280
2 A/IOWA/1/2006	H1N1v (beta)	20	640	20	1280	80	2560	20
3 A/WISCONSIN/28/2011	H1N1v (gamma)	5120	2560	2560	5120	2560	320	160
4 A/MISSOURI/12/2012	H1N1v (gamma)	5120	5120	5120	5120	2560	1280	1280
5 A/MINNESOTA/33/2014	H1N1v (gamma)	5120	5120	2560	5120	5120	160	640
6 A/OHIO/09/2015	H1N1v (gamma)	<	80	20	20	80	5120	20
TEST ANTIGEN								
7 A/IOWA/39/2015	H1N1v (gamma)	160	80	80	40	1280	640	320

Indicates comparison to CVV

* Post-vaccine immune serum pool from adult (19-49 yrs) vaccinees

Compared to A/California/07/2009 there were 46 amino acid changes in the HA protein.

Genetic analysis of the hemagglutinin gene of the H1N1v virus detected the presence of a D222G amino acid change in the receptor binding site (D225G in H3 numbering).

Substitutions at this position (D222N or G) have been detected occasionally in H1N1 viruses isolated directly from swine, particularly in viruses of the H1N1pdm09 lineage.

In humans, the D222G substitution has been detected in viruses from severe and fatal cases of A(H1N1)pdm09 infection, although D222G has also been found in humans with mild disease.

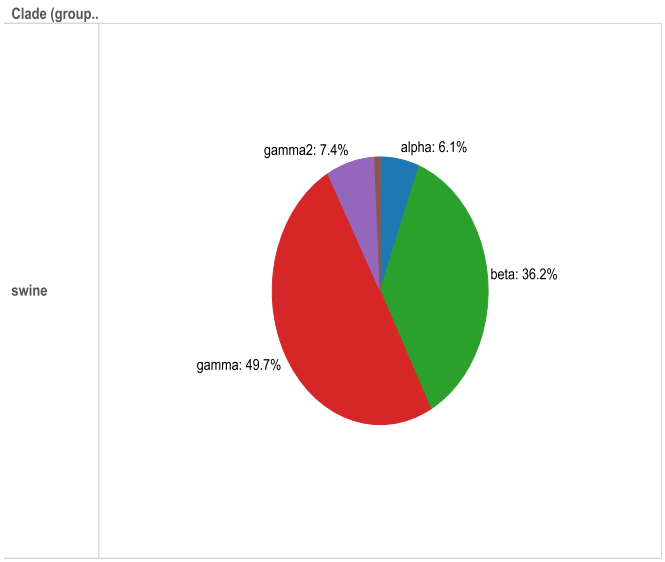
- This substitution may occur during the course of infection in humans or during serial passage in laboratory host systems.
- In humans, this substitution is detected more often in A(H1N1)pdm09 viruses isolated from the lower respiratory tract, which is a site more likely to be sampled in severe/fatal cases. This H1N1v virus was sampled from the lower respiratory tract.

While the D222G substitution can be associated with more severe disease, its public health significance remains unclear.

Genetic analysis of the hemagglutinin gene of this H1N1v virus also identified a substitution at position 155 (G155E) within immunodominant antigenic site B.

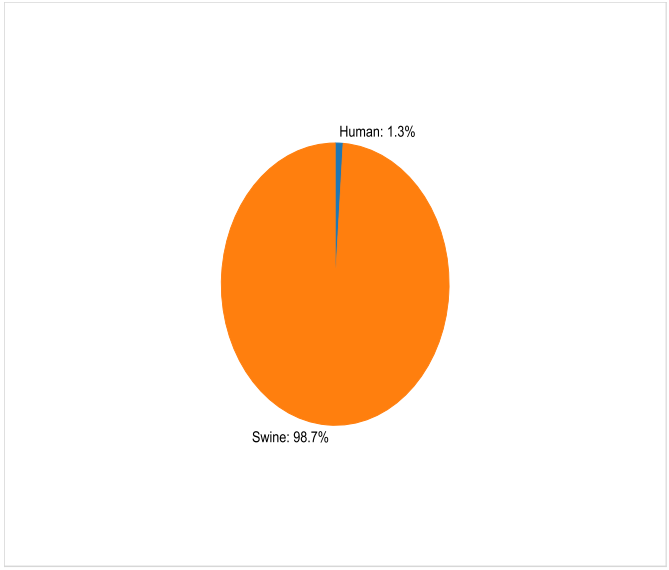
- Serologic studies have indicated that human A(H1N1)pdm09 viruses with this change show reduced binding to immune sera raised to the vaccine virus A/California/07/2009.
- Mutations as this position have been detected in H1N1 viruses isolated from swine.

Clade



Clade
alpha
gamma
ND
beta
gamma2

Host



Host
Human
Swine

Allele
E

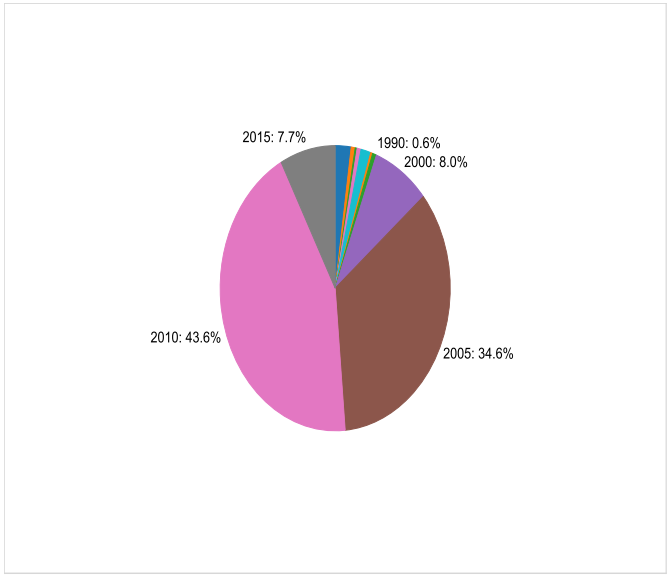
Residue
155

312 US sequences with 155E

Region

Who Region
PAHO

Year



Collection Year (bin)
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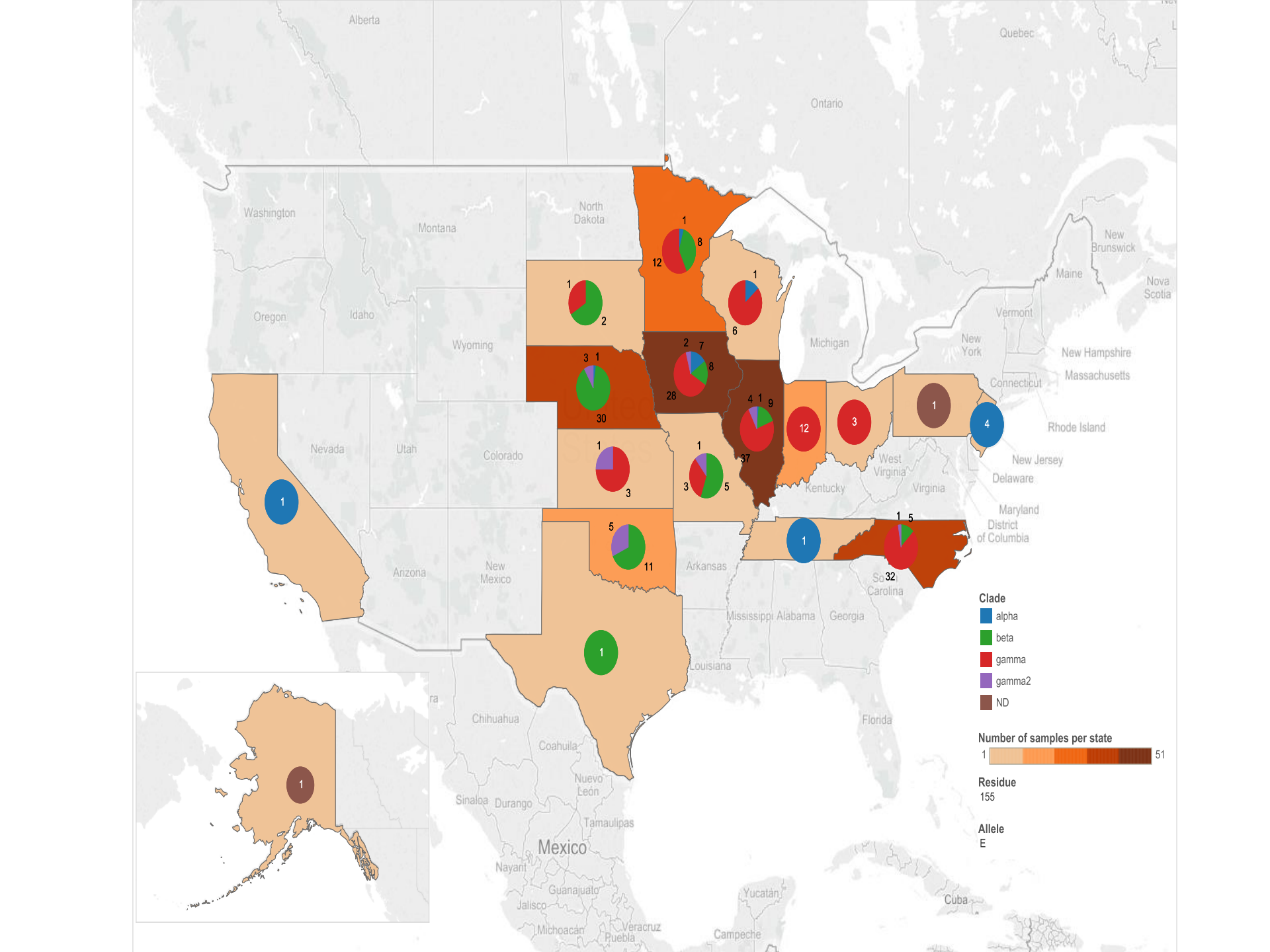
1935 1945 1955 1965 1975 1985 1995 2005 2015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New Brunswick
Maine
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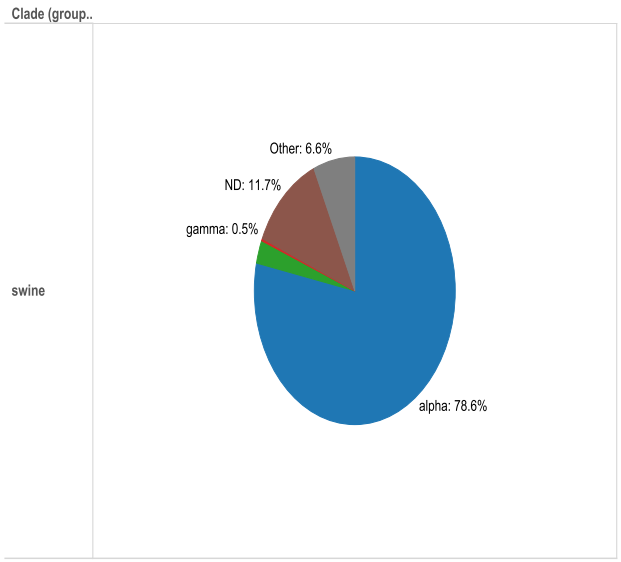
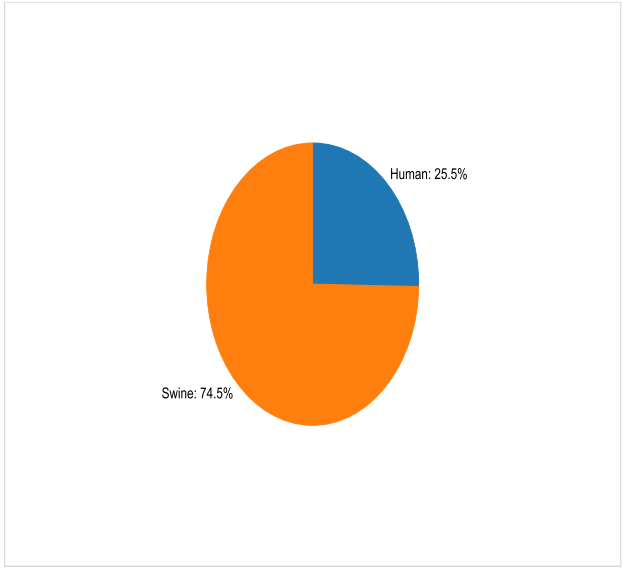
New Hampshire
Massachusetts
Connecticut
Rhode Island
New Jersey
Delaware
Maryland
District of Columbia
Nevada
Utah
Colorado
Arizona
New Mexico
Kentucky
West Virginia
Virginia
Arkansas
Mississippi
Alabama
Georgia
Florida
Louisiana
Chihuahua
Coahuila
Nuevo León
Sinaloa
Durango
Tamaulipas
Mexico
Nayarit
Guanajuato
Jalisco
Michoacán
Veracruz
Puebla
Yucatán
Campeche
Cuba
Clade
alpha
beta
gamma
gamma2
ND
Number of samples per state
1
51
Residue
155
Allele
E

Clade



Clade
alpha
beta
gamma
ND
Other

Host



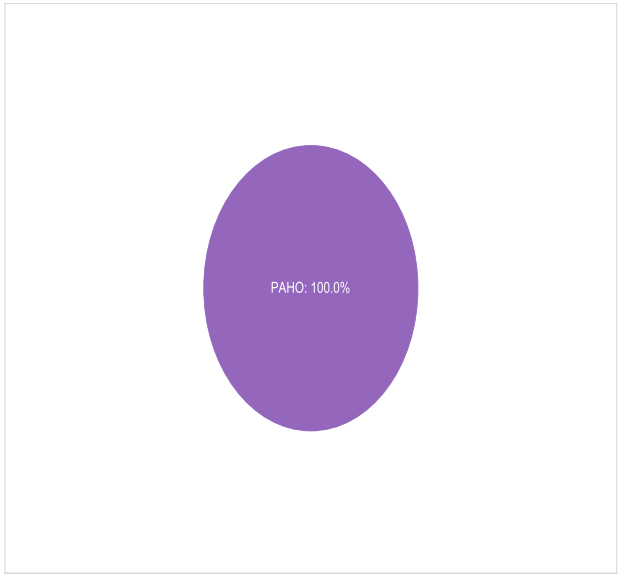
Host
Human
Swine

Allele
G

Residue
222

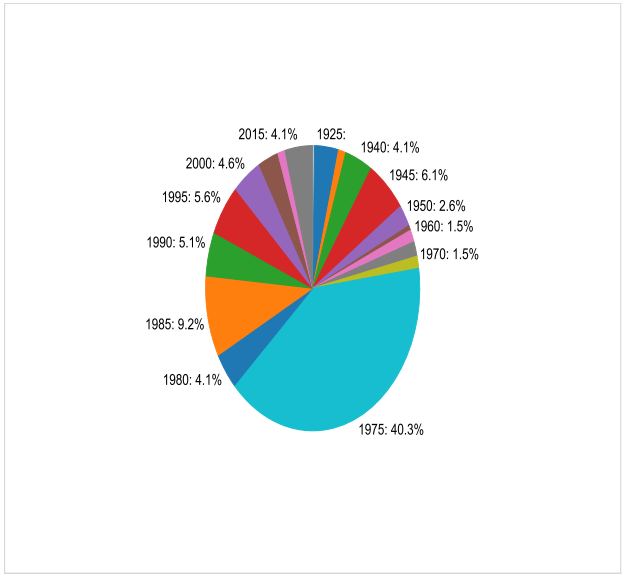
196 US sequences with 222G

Region



Who Region
PAHO

Year



Collection Year (bin)
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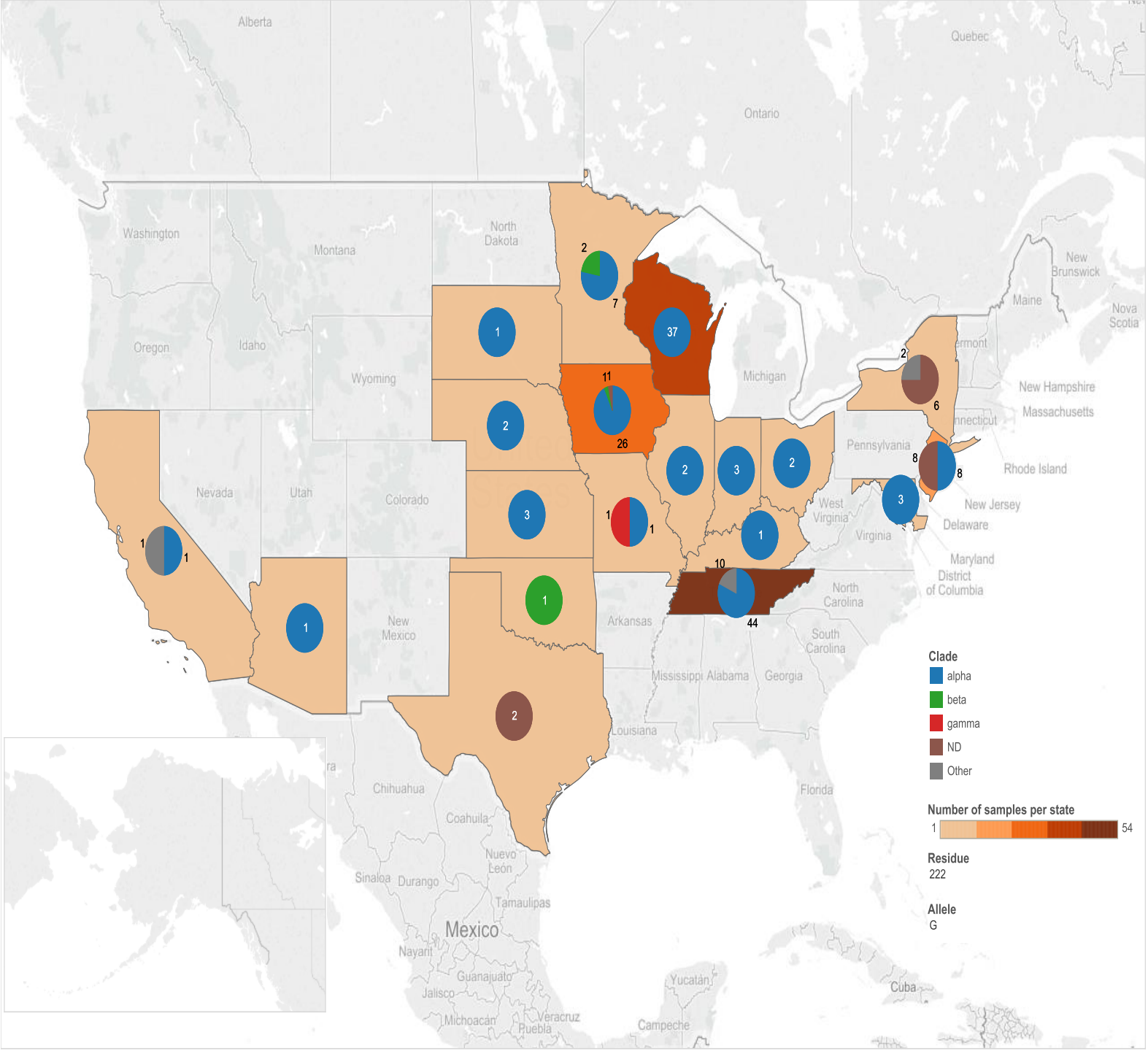
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Mississippi
Alabama
Georgia
Louisiana
Florida
South Carolina
North Carolina
Virginia
West Virginia
Pennsylvania
New Jersey
Delaware
Maryland
District of Columbia
Rhode Island
Massachusetts
New Hampshire
Maine
Nova Scotia
New Brunswick
Chihuahua
Coahuila
Nuevo León
Sinaloa
Durango
Tamaulipas
Mexico
Nayarit
Guanajuato
Jalisco
Michoacán
Veracruz
Puebla
Campeche
Yucatán
Cuba
2
7
37
1
11
26
2
3
1
1
1
2
3
2
1
10
44
1
1
2
6
8
8
3
Clade
alpha
beta
gamma
ND
Other
Number of samples per state
1
54
Residue
222
Allele
G

Ongoing studies

Generation of Ohio/9 CVV

- ferret antisera production/antigenic characterization

Generation of Ohio/9 CVV without 155E

- ferret antisera production/antigenic characterization

Pathotyping in ferrets

- Ohio/9 vs. related H1v viruses (without 155 or 222 subst.)

Vaccine efficacy in ferret model vaccinated with current seasonal vaccine

- challenge ferrets with Ohio/9 wt

Acknowledgements

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Influenza Division

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