

The Mother of All Pandemics

100 Year Anniversary of the 1918 H1N1 Pandemic

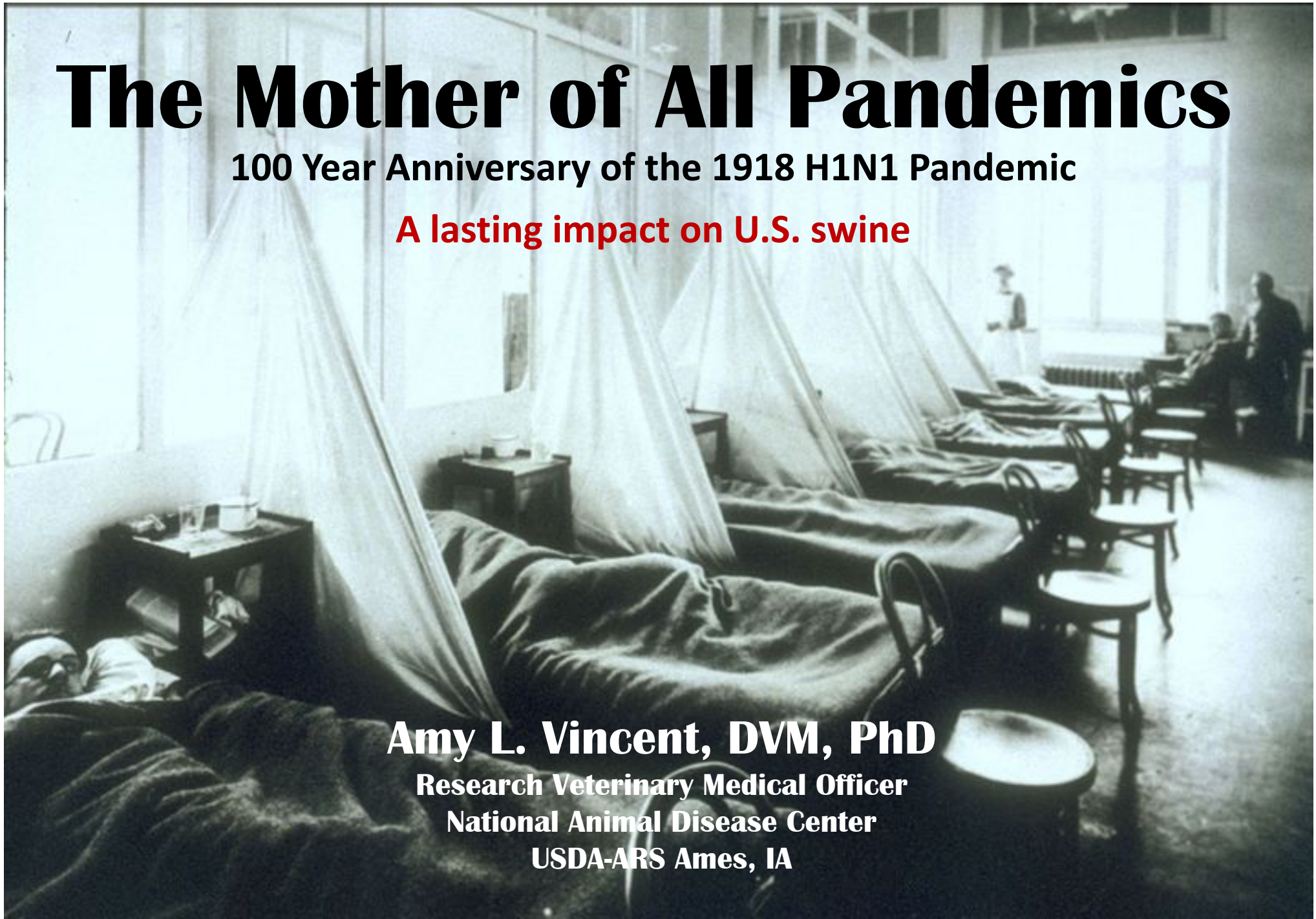
A lasting impact on U.S. swine

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Presentation Overview

- 1918 Spanish Flu – the “Mother of all Pandemics”
- Influenza ecology
- Evolution of IAV in swine
- Current genetic diversity of IAV in US/North America
- Antigenic consequence of IAV diversity
- Human-swine interface
- Why does a century old pandemic matter?



WE REMEMBER. WE PREPARE.

1918-19 - Three Waves

- 1st Wave - Late 1917, mostly early 1918.
 - A few sporadic reports, appeared to be milder
- March 1918 - Fort Riley, Kansas.
 - Spread among military camps and among troops in World War I
- By fall 1918 into winter 1919, the disease began sickening civilians in most U.S. cities and towns.
 - **2nd Wave** was the most devastating.
 - Patriotic marches and military recruiting events
 - Some cities began banning all public gatherings
- Resolution by Congress for \$1,000,000 to fight flu.
 - Doctors and scientists thought cause was a bacteria and tried making bacterins as vaccines.
- Heavy toll on troops in Europe, so more troops sent by ship.
 - Ideal situation to amplify and spread flu.
- September 1918 reached the peak of the outbreak & mortalities.
- In November, Germany surrendered and troops were back on ships to return home, Armistice Day celebrations, etc., so the spread continued.
- A milder 3rd wave occurred in early 1919.



1918 H1N1 – the toll

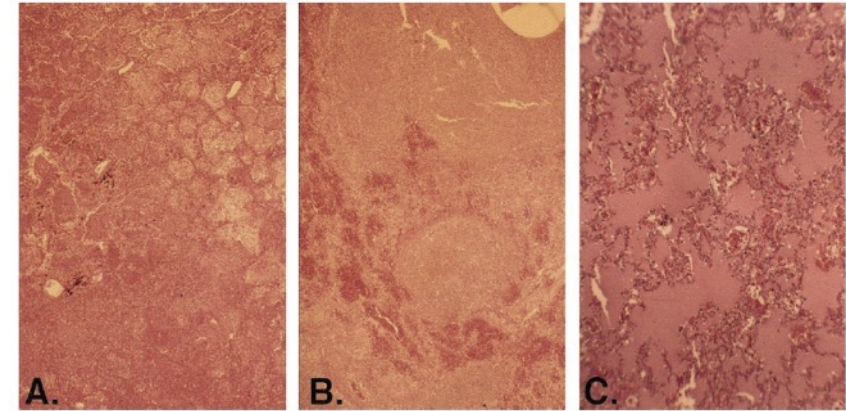
- Overall estimates up to 1/5 of the world's population at the time were infected
- Between 20-50 million deaths (some estimates up to 100 million)
 - 18 million killed in WWI



Different stages of skin coloration as seen during the 1918 influenza pandemic characterized as “heliotrope” or deep blue cyanosis. Reproduced with permission from the Lancet archives.
Shanks, D. Travel Medicine and Infectious Disease 2015 13, 217-222 DOI: (10.1016/j.tmaid.2015.05.001)

Presentation of severe 1918 cases

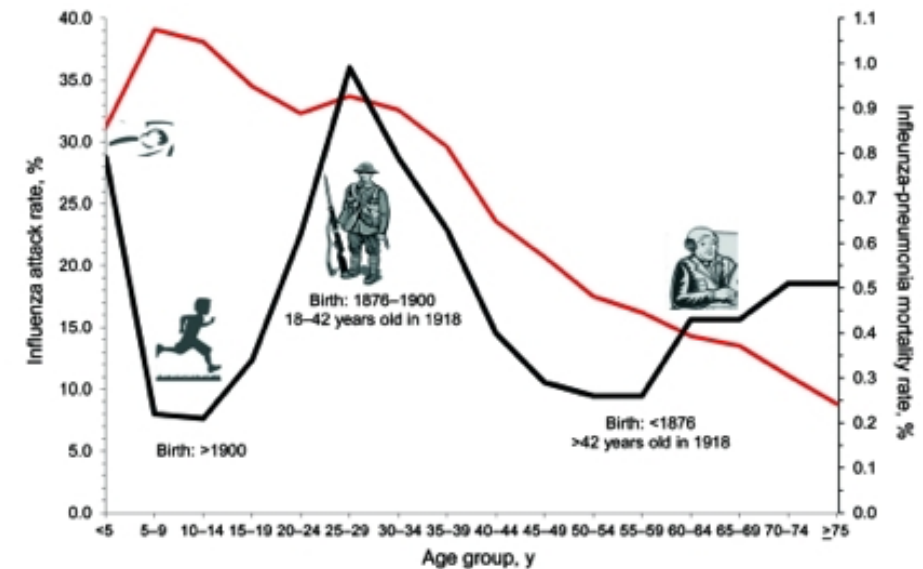
- Clinical presentation in severe cases:
 - Epistaxis
 - Cyanosis followed by rapid deterioration and death
- Severe histopathology described
 - Pulmonary hemorrhage and edema
 - Epithelial necrosis
 - Vascular necrosis
- Severe necrotizing hemorrhagic bronchopneumonia with or without evidence of bacteria
- Acute respiratory distress syndrome (ARDS)-like lesions
 - Alveolar edema and hemorrhage



Morens, DM; *The 1918 Influenza Pandemic: Insights for the 21st Century*, *The Journal of Infectious Diseases*, Volume 195, Issue 7, 1 April 2007, Pages 1018–1028, <https://doi.org/10.1086/511989>

What made 1918 H1N1 so pathogenic?

- The reasons for the severity of 1918 H1N1 remains a mystery
 - “W-Shaped” Mortality Curve
 - Unique virulence
 - Reconstructed 1918 H1N1 viruses not overly revealing in experimental challenges
 - Different variants of H1N1 circulating
 - Additional pathogens – secondary bacteria
 - Global migration (war) and harsh conditions
- Antigenic sin or antigenic imprinting



Shanks GD, Brundage JF. Pathogenic Responses among Young Adults during the 1918 Influenza Pandemic. *Emerging Infectious Diseases*. 2012;18(2):201-207. doi:10.3201/eid1802.102042.

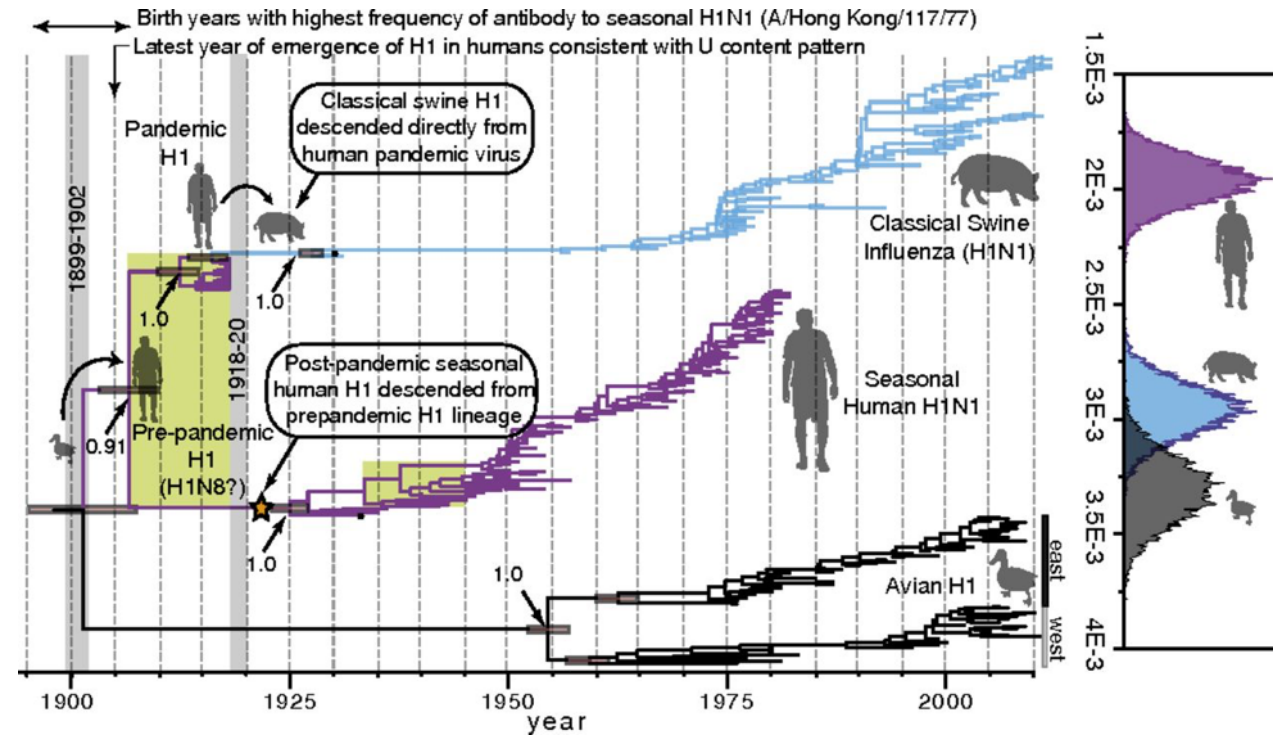
Influenza in humans prior to 1918



Genesis and pathogenesis of the 1918 pandemic H1N1 influenza A virus

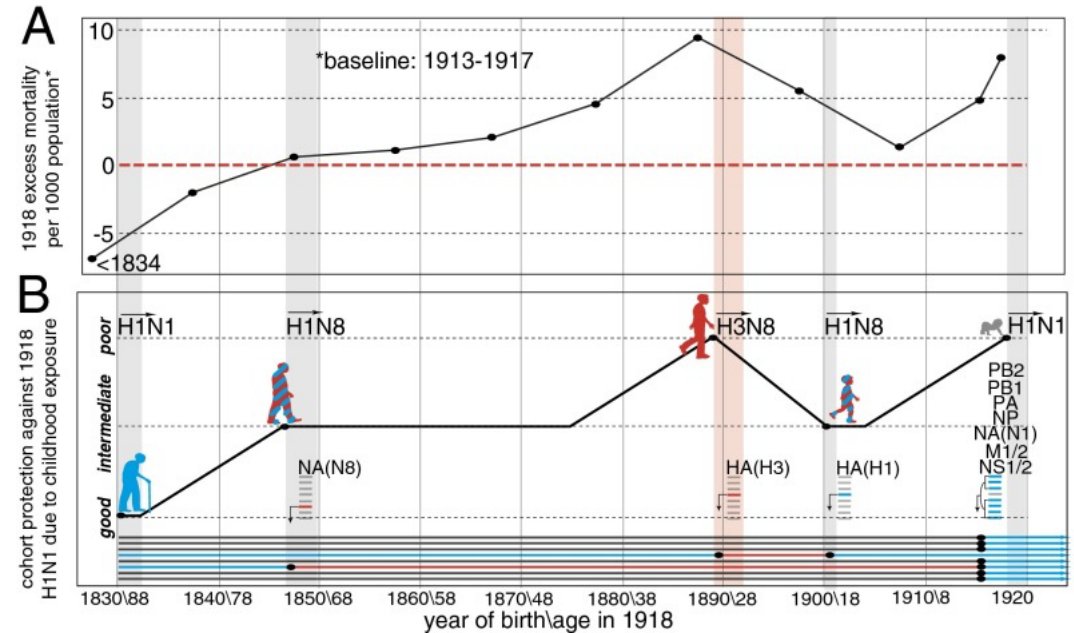
Michael Worobey^{a,1}, Guan-Zhu Han^a, and Andrew Rambaut^{b,c,d}

^aDepartment of Ecology and Evolutionary Biology, University of Arizona, Tucson, AZ 85721; ^bInstitute of Evolutionary Biology and ^cCentre for Infection, Immunity, and Evolution, University of Edinburgh, Edinburgh EH9 3JF, United Kingdom; and ^dFogarty International Center, National Institutes of Health, Bethesda, MD 20892



Historical evidence for prior pandemics

- 1830s H1N1
- 1850s H1N8
- 1890s H3N8
- 1900s H1N8: This H1 diverged to modern classical swine and human seasonal (pre-2009)

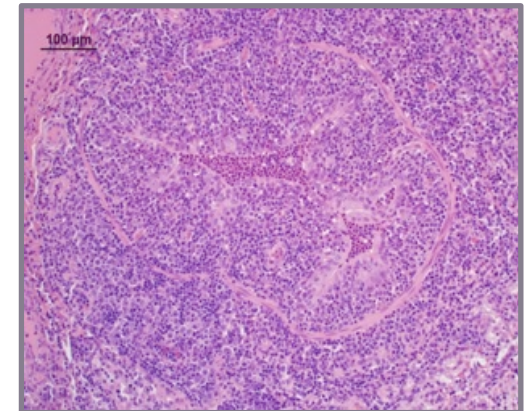


VAERD

Vaccine-Associated Enhanced Respiratory Disease

- Mismatched challenge to whole inactivated virus vaccine
 - Same subtype, but antigenically mismatched
 - H1 and H3 models
- Whole Inactivated Virus (WIV) + Oil-in-Water Emulsion Adjuvant
 - Other adjuvants did not induce VAERD
- Mismatched passive antibodies from vaccinated dams
- HA subunit protein with adjuvant
- Microscopic lesions:
 - Interlobular edema
 - Alveolar edema & hemorrhage
 - Interstitial pneumonia
 - Peribronchiolar lymphocytic cuffing
 - Suppurative bronchitis/alveolitis
 - Lymphocytic subepithelial infiltration
- WIV induces cross-reacting whole-virus antibodies that **do not cross-react by HI or SN.**

VAERD



Swine Model of Antigenic Imprinting

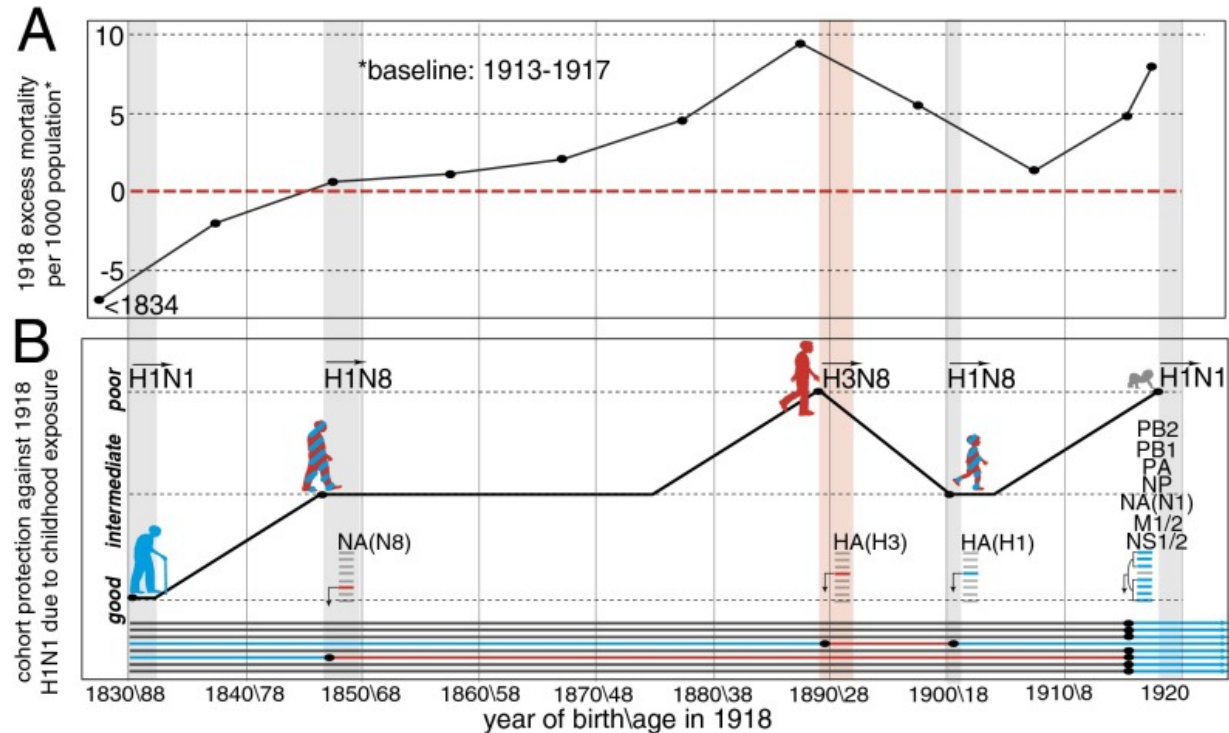


Genesis and pathogenesis of the 1918 pandemic H1N1 influenza A virus

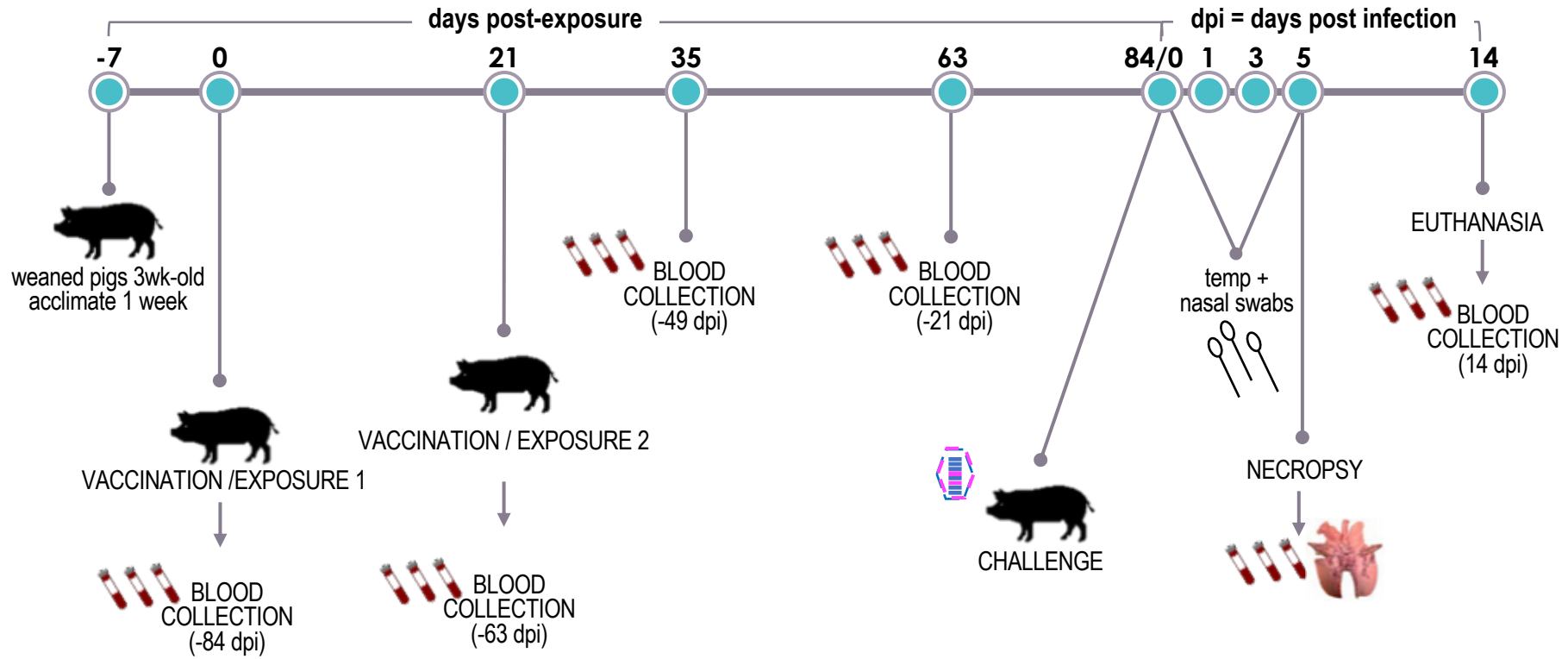
Michael Worobey^{a,1}, Guan-Zhu Han^a, and Andrew Rambaut^{b,c,d}












^aDepartment of Ecology and Evolutionary Biology, University of Arizona, Tucson, AZ 85721; ^bInstitute of Evolutionary Biology and ^cCentre for Infection, Immunity, and Evolution, University of Edinburgh, Edinburgh EH9 3JT, United Kingdom; and ^dFogarty International Center, National Institutes of Health, Bethesda, MD 20892

Can the sequence of exposures misdirect the immune response and recapitulate the enhanced lung pathology previously only seen with WIV in our VAERD models?

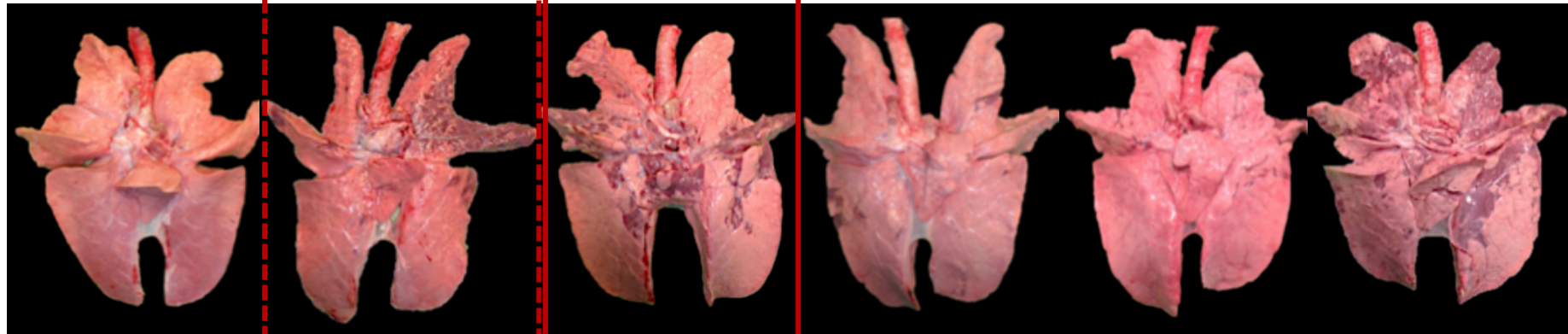
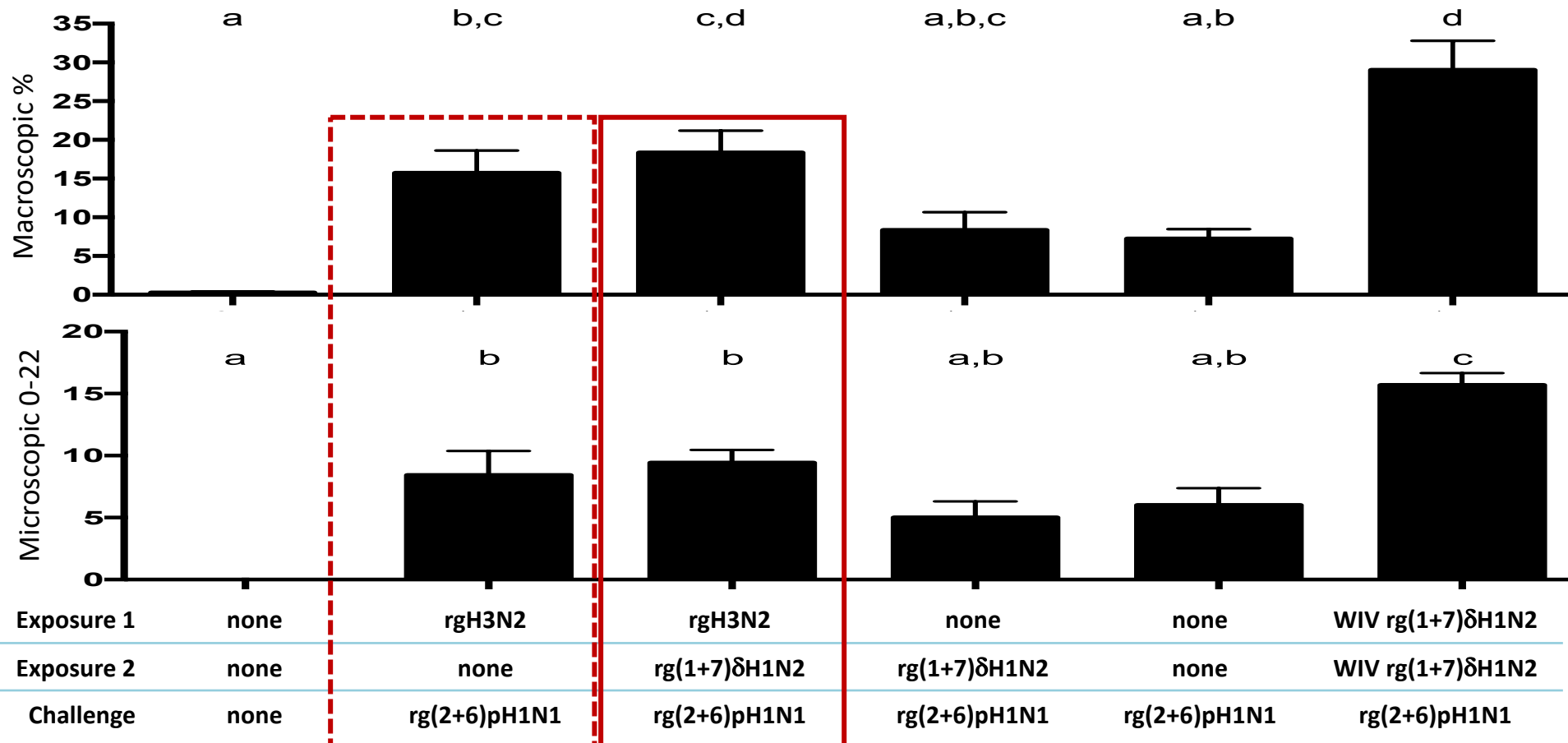


Study Design



Group	Exposure 1	Exposure 2	Challenge	Nec1	Nec2
1	None	None	None	5	-
2	rgH3N2 	None	rg(2+6)pH1N1 	10	5
3	rgH3N2 	rg(1+7)δH1N2 	rg(2+6)pH1N1 	10	5
4	None	rg(1+7)δH1N2 	rg(2+6)pH1N1 	10	5
5	None	None	rg(2+6)pH1N1 	10	5
6	WIV rg(1+7)δH1N2 	WIV rg(1+7)δH1N2 	rg(2+6)pH1N1 	10	-

Macroscopic and microscopic Pneumonia Lesions



Modern History of Flu



Bird Flu

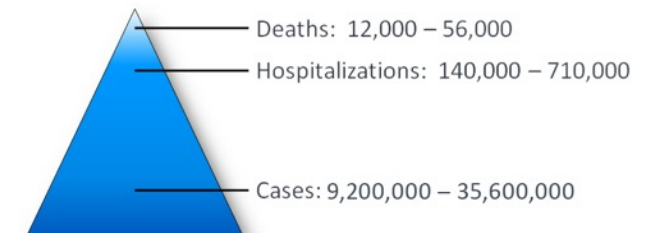
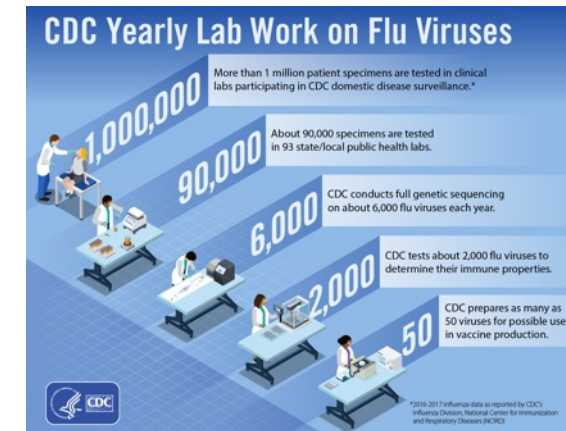


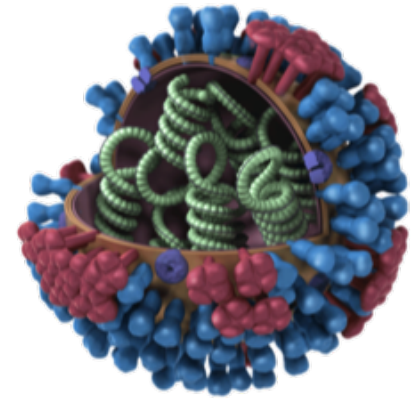
- 1931 IAV first isolated from pigs
- 1933 IAV first isolated from humans
- 1935 first influenza vaccine
- 1952 WHO began global surveillance network
- 1956 CDC became WHO collaborating center
- 1957 H2N2 Asian flu pandemic
- 1968 H3N2 Hong Kong flu pandemic
- 1973 WHO selects first vaccine strain
- 1976 Fort Dix “swine flu” scare
- 1977 H1N1 Russian flu re-emerges
- 1986 First WHO vaccine strain composition meeting
- 1997 First H5N1 AIV outbreak in humans
- 2006 First Pre-pandemic (animal) candidate vaccine strain
- 2009 H1N1pdm09 pandemic from swine lineages
- 2013 First H7N9 AIV outbreak in humans

Today – Seasonal Influenza in Humans



- The 1918 Spanish flu pandemic led to strengthening of national and global public health organizations.
- World Health Organization – Influenza committee began in 1947.
- US DHHS dedicates a major portion of its budget to influenza (NIH, FDA & **CDC**).
- CDC began in 1942, established an influenza unit in 1957.
 - ~200,000 Americans hospitalized for ILI each year
 - Annual deaths range in the 10,000s in the USA
 - Greater toll in developing countries
 - Very young, very old, pregnant, immunocompromised, or pre-existing medical conditions at higher risk
 - CDC major contributor to WHO global influenza program





Influenza ecology & evolution

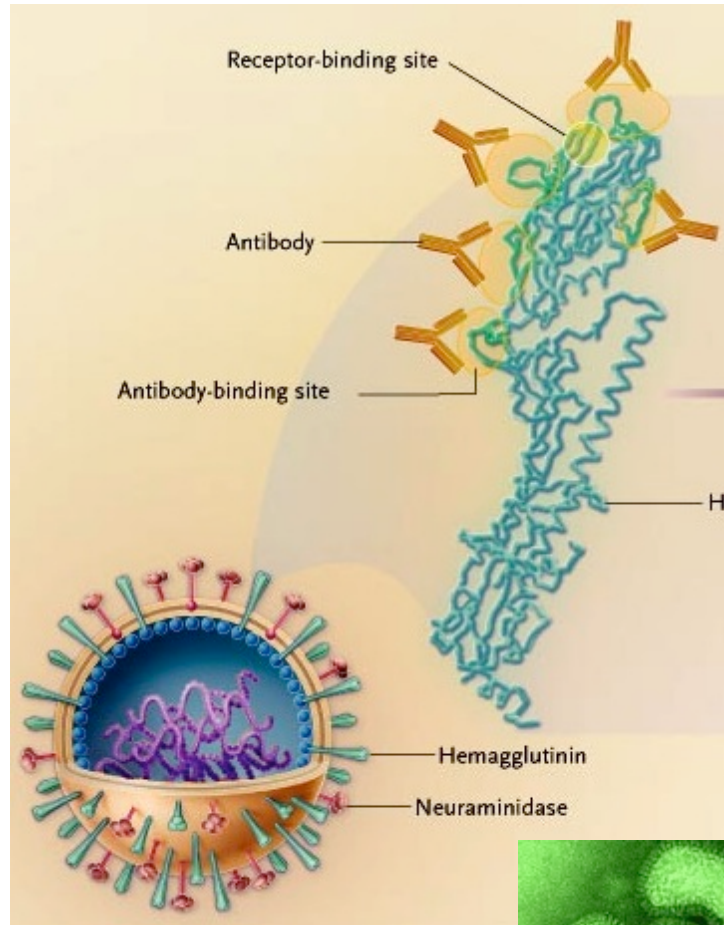
100 years, why is influenza A virus still a problem?

Clinical Disease influenza in swine

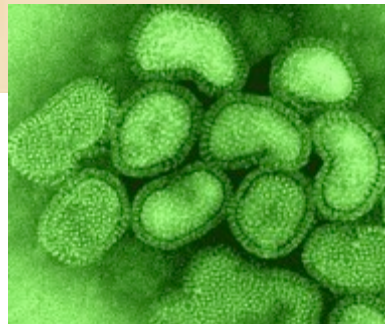
- High morbidity, low mortality
- All ages affected, typically more severe in younger growing pigs
- Infection limited to respiratory tract
 - Cough, dyspnea, fever, nasal discharge, inappetence
- Self-limiting in most uncomplicated cases
- Predisposes to secondary bacterial infections and is a component of porcine respiratory disease complex



Influenza A Virus



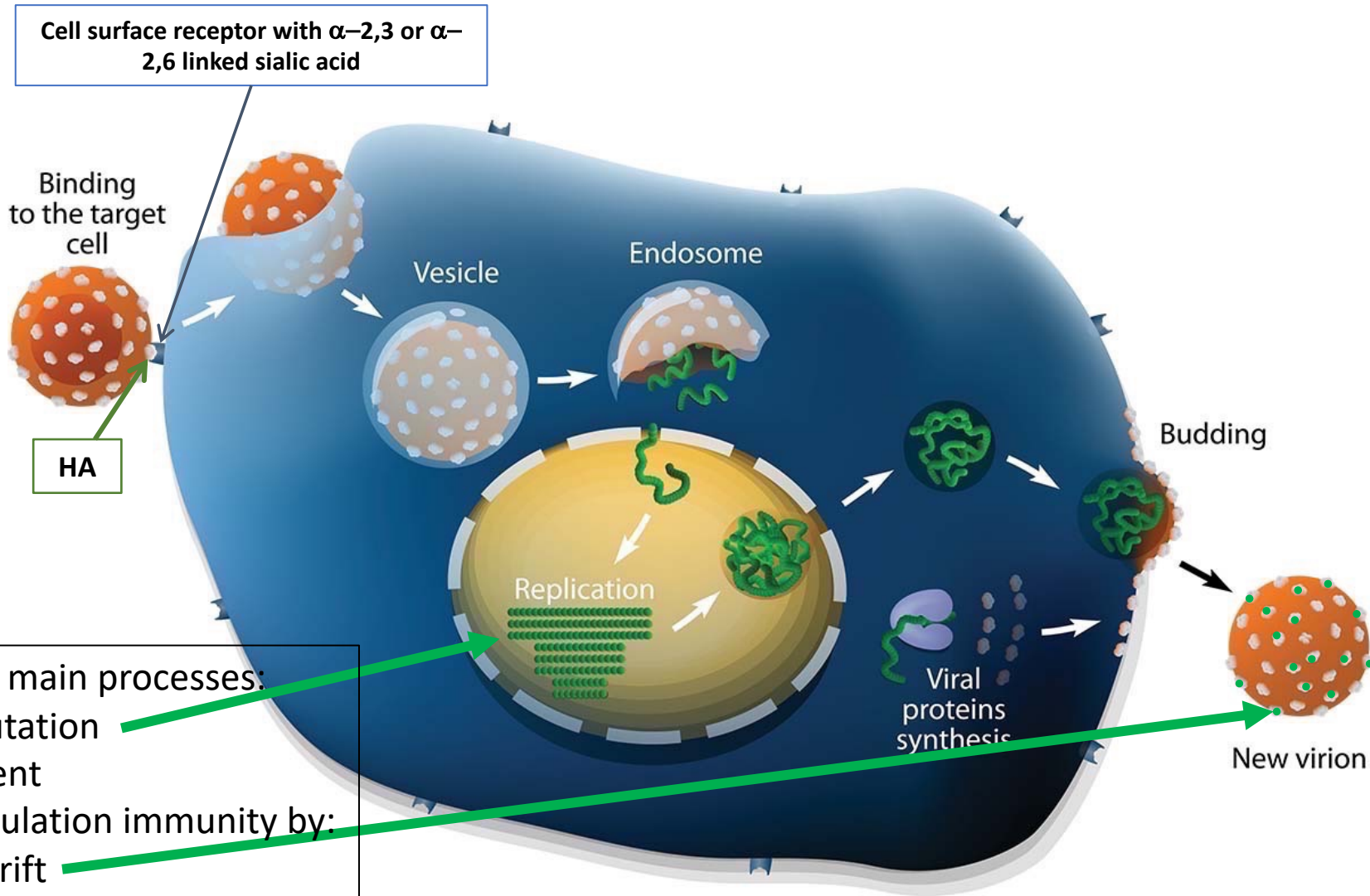
Treanor J. N Engl J Med 2004;350:218-220



<http://web.uct.ac.za/depts/mmi/stannard/fluivirus.html>

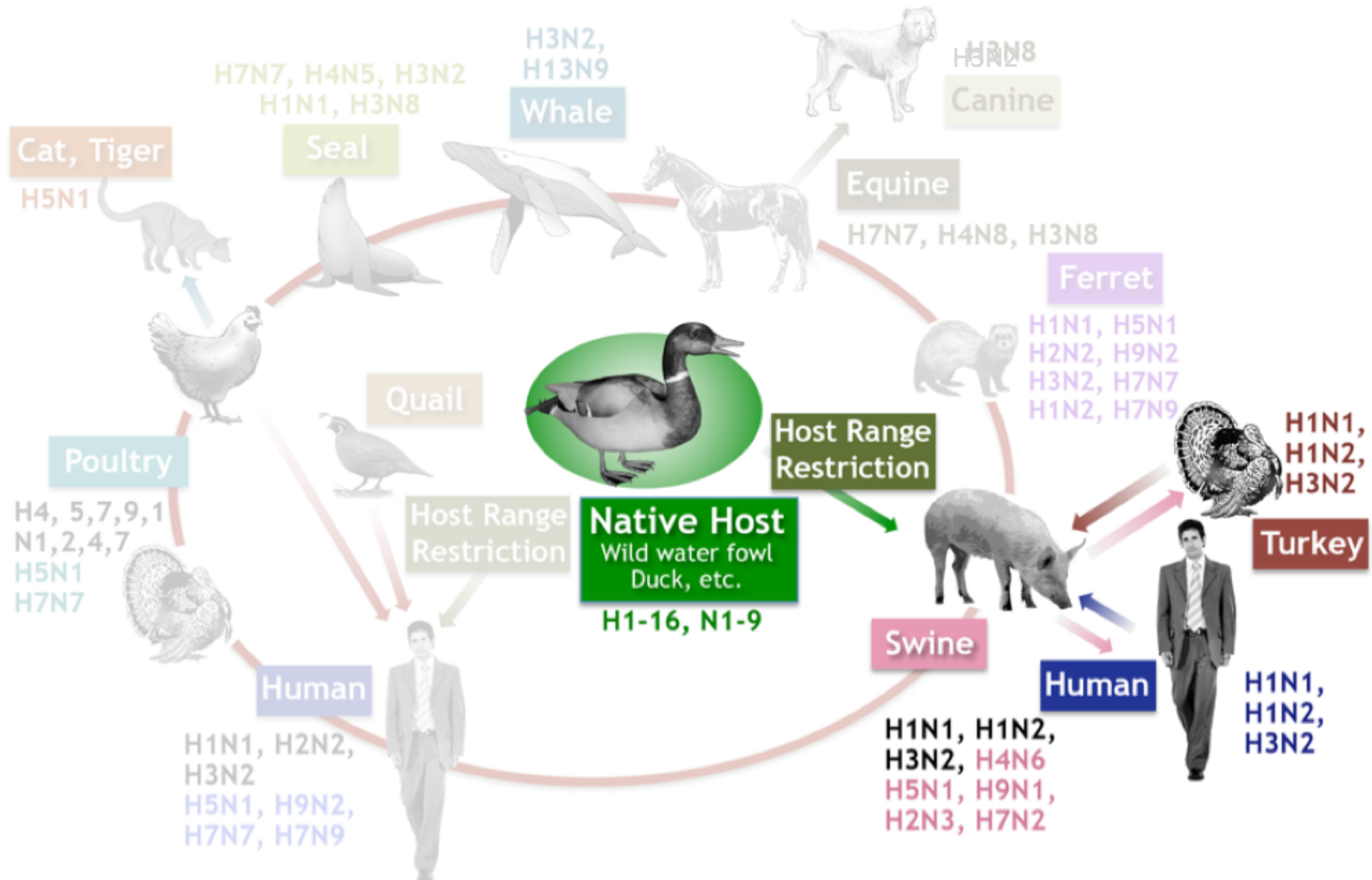
- Orthomyxovirus
- Negative strand RNA genome
- **Segmented genome**
 - 8 segments
 - Encodes 10 (12) proteins
- Enveloped
- 2 major surface glycoproteins
 - Hemagglutinin (HA) – 18 subtypes
 - Receptor binding site
 - Neuraminidase (NA) – 11 subtypes
 - Enzyme to release budding progeny virions

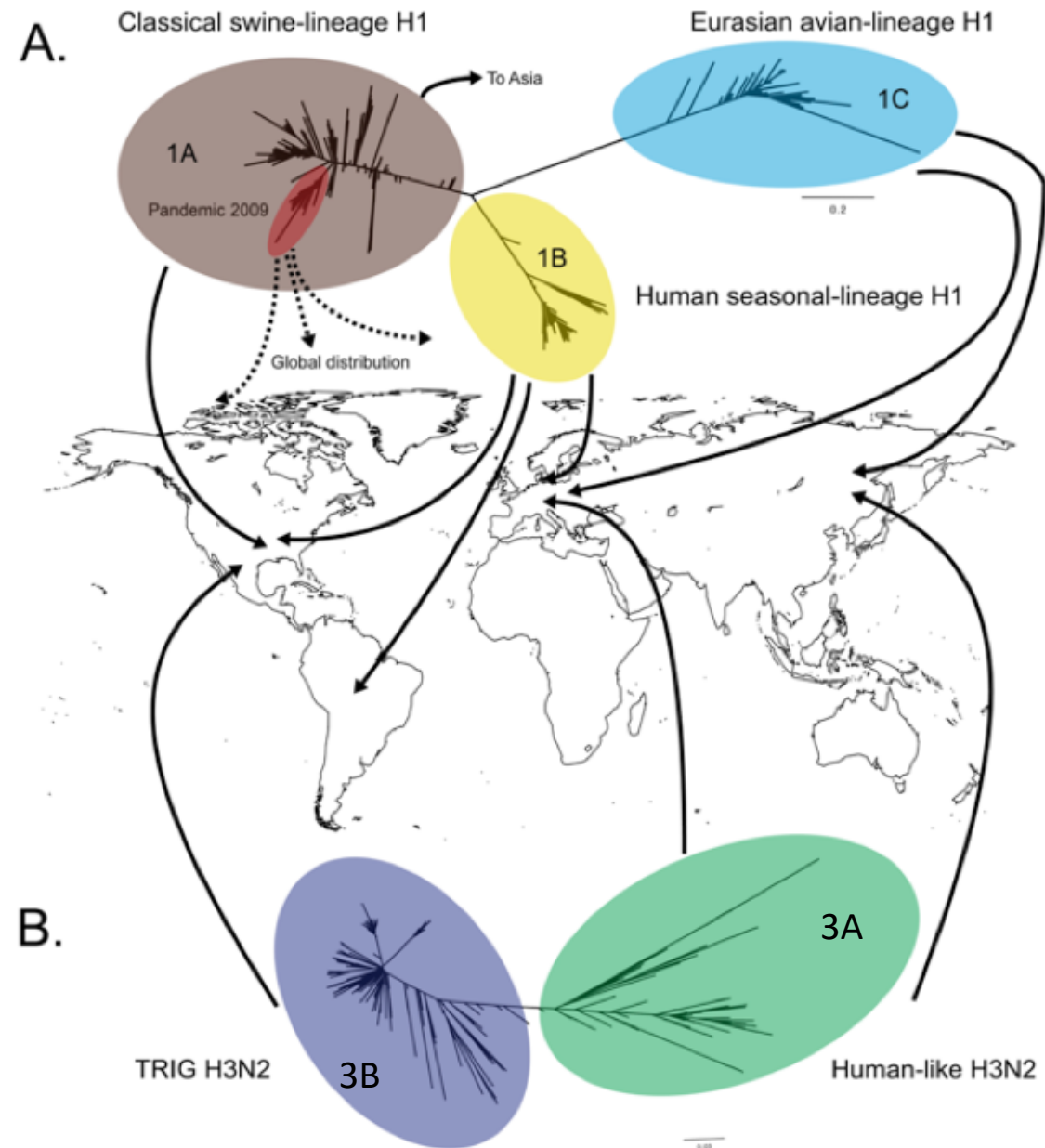
INFLUENZA VIRAL LIFE CYCLE



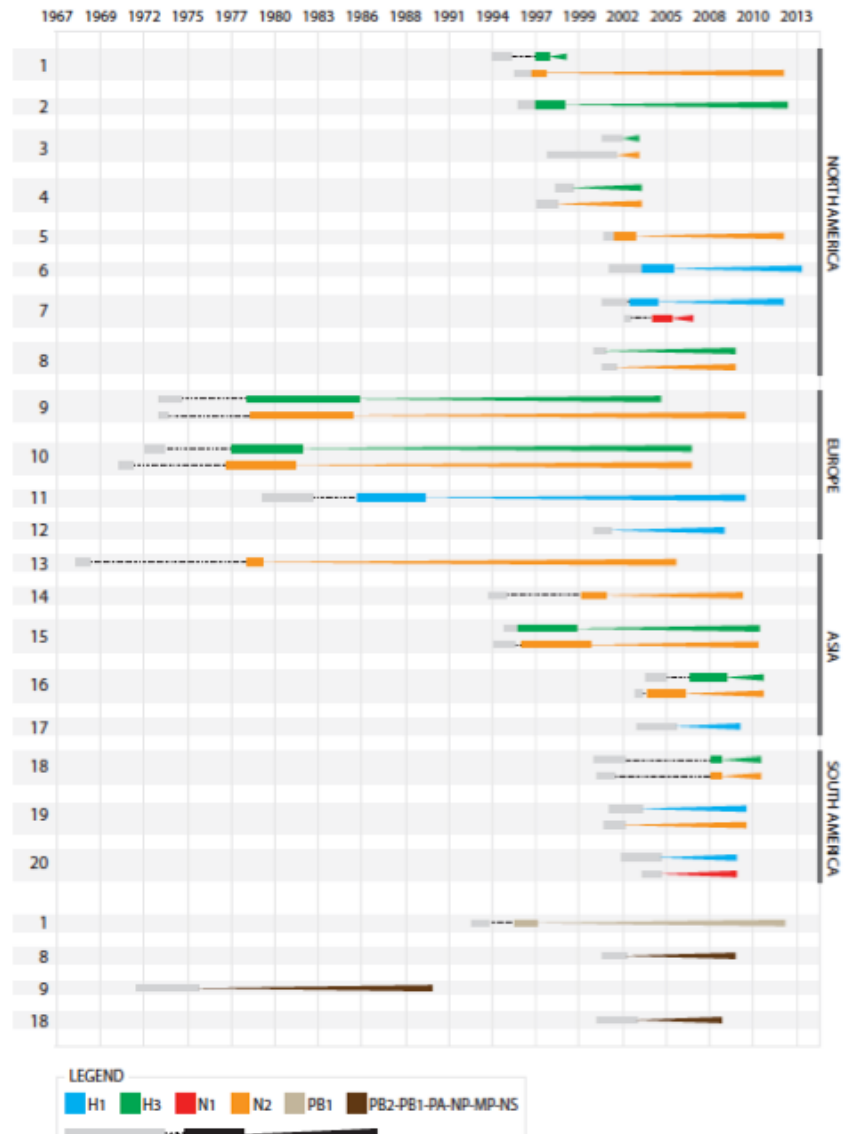
- IAV evolves by 2 main processes:
 - Genetic mutation
 - Reassortment
- IAV escapes population immunity by:
 - Antigenic drift
 - Antigenic shift

Pigs are a natural host for IAV

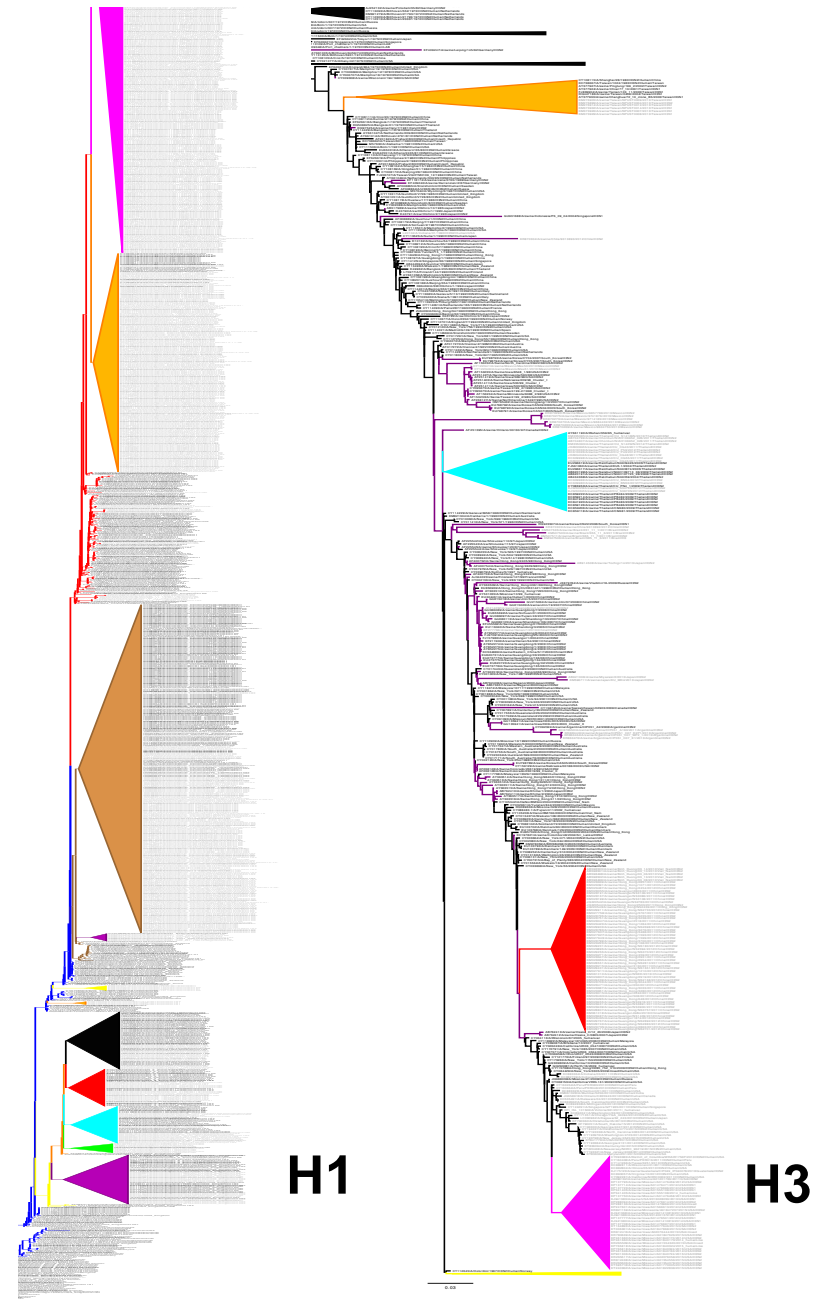




Diversity of swine IAV shaped by human IAV

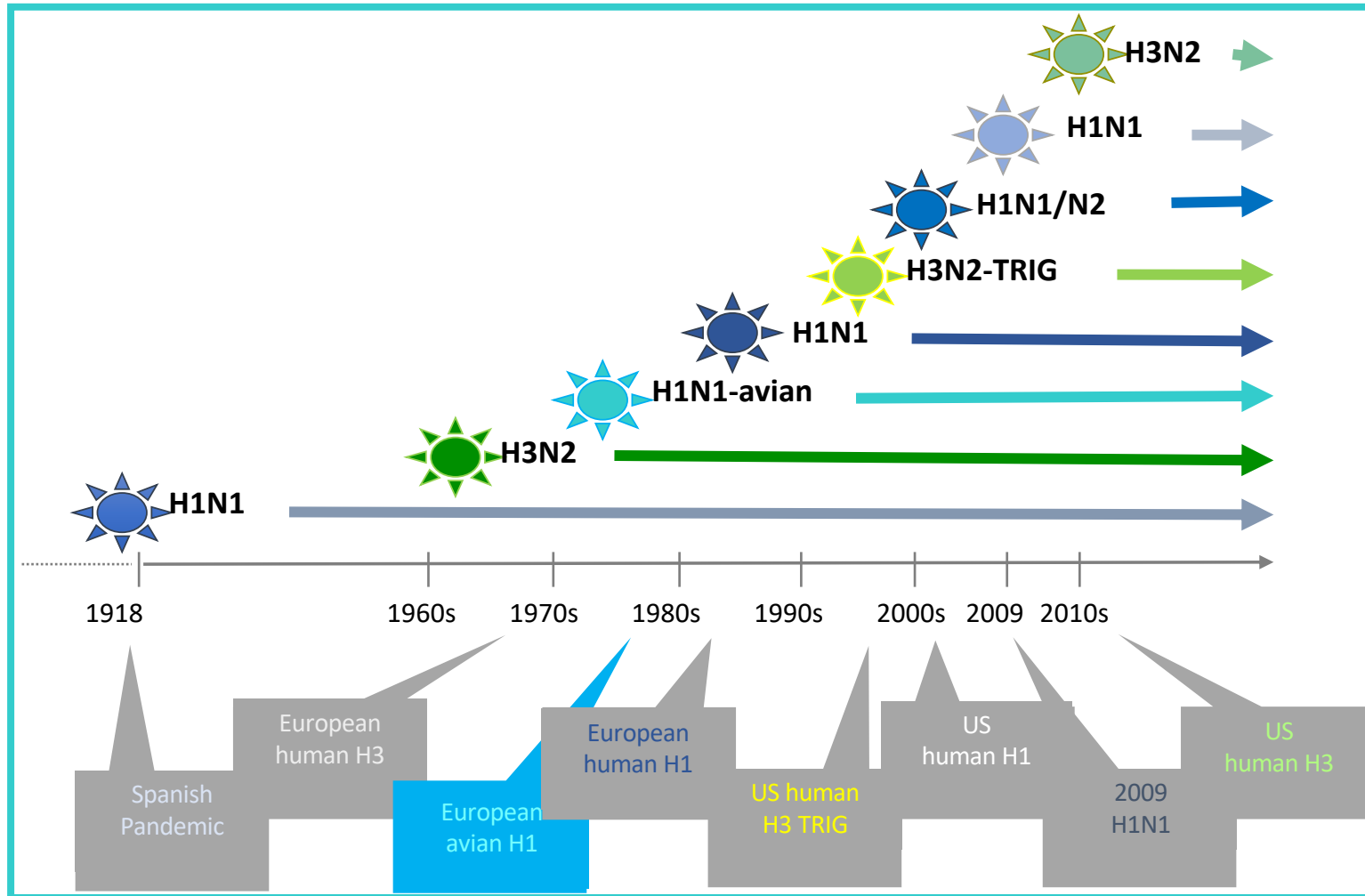


M. I. Nelson, et al. 2014

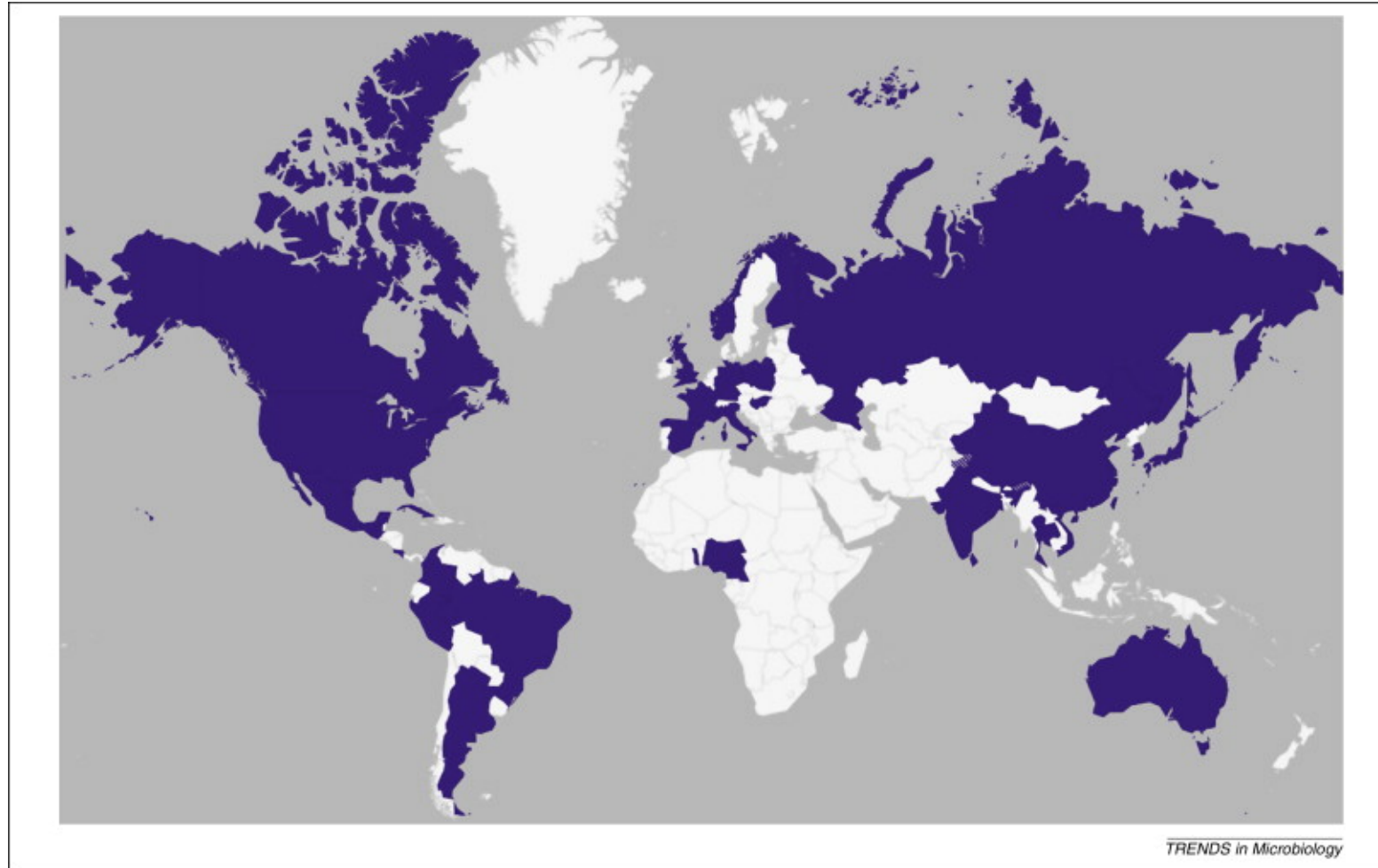


T.K. Anderson²¹

Timeline of IAV introductions in swine

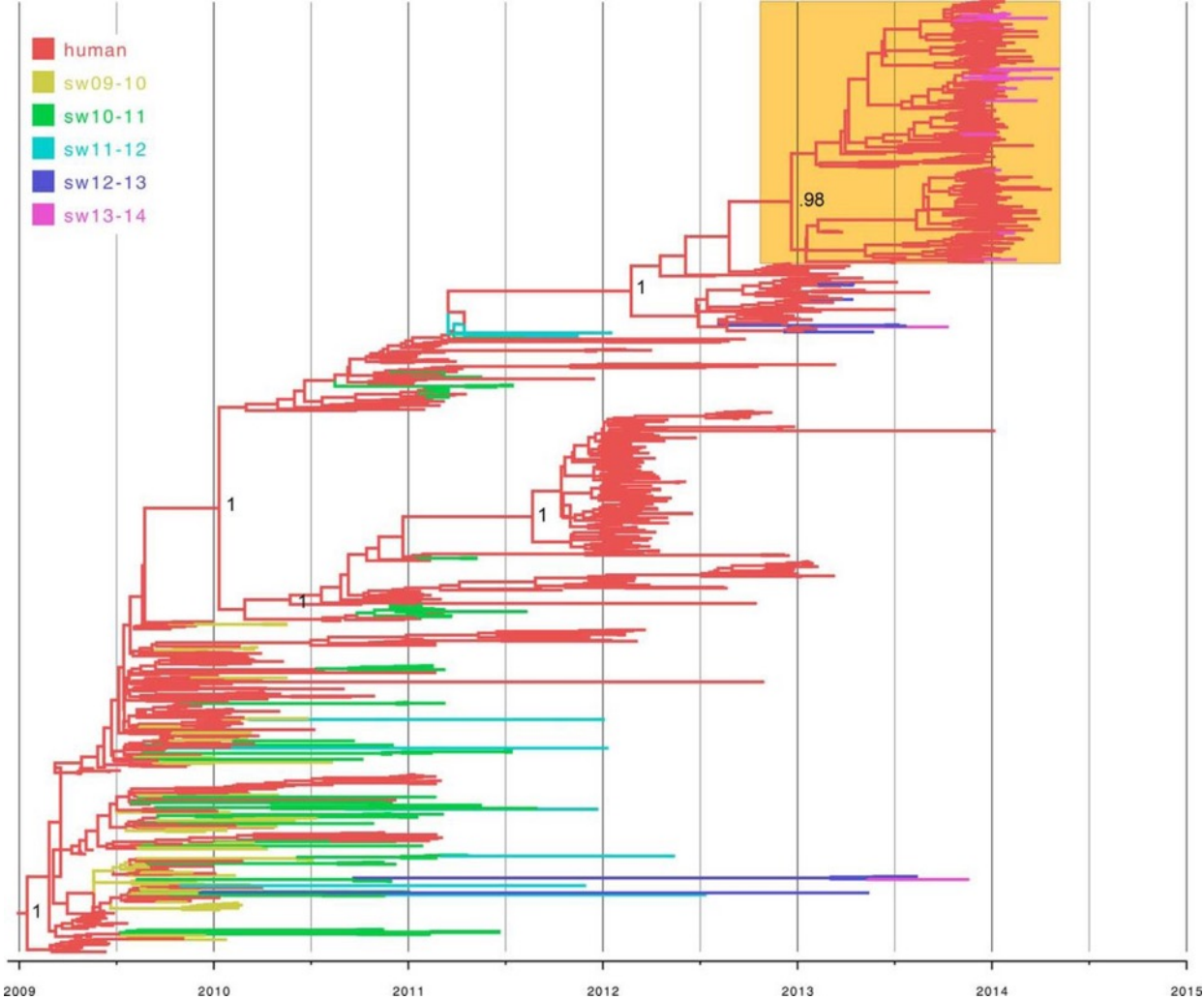


Countries with H1N1 pdm09 in pigs



Nelson and Vincent, Trends Microbiol. 2015

Continued transmission of H1N1 pdm09 from humans to pigs



Martha I. Nelson et al. *J. Virol.* 2015;89:6218-6226

Journal of Virology

Journals.ASM.org | Copyright © American Society for Microbiology. All Rights Reserved.



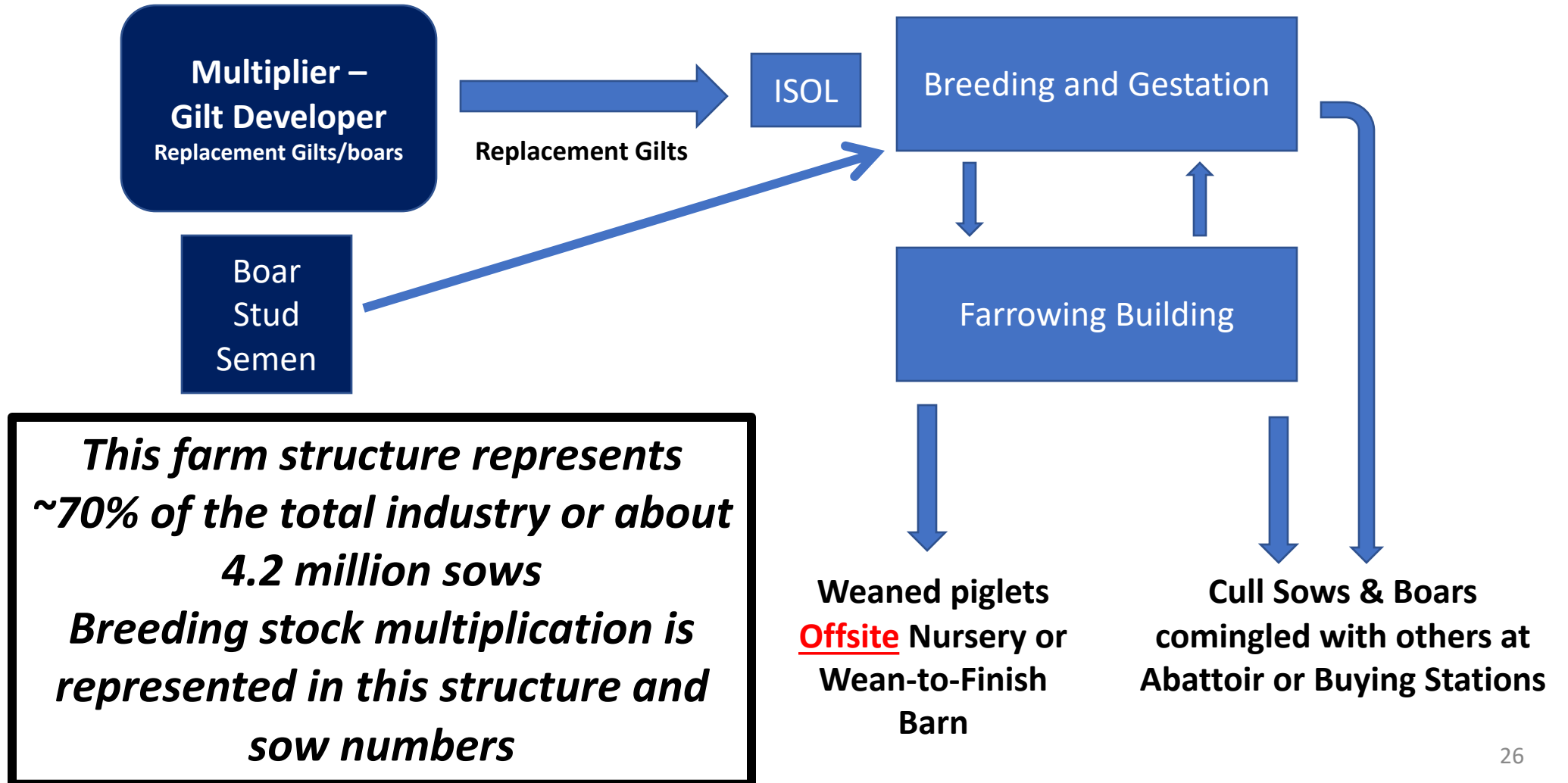


Production practices & the impact on Influenza in swine



Typical pig flow in a commercial farm

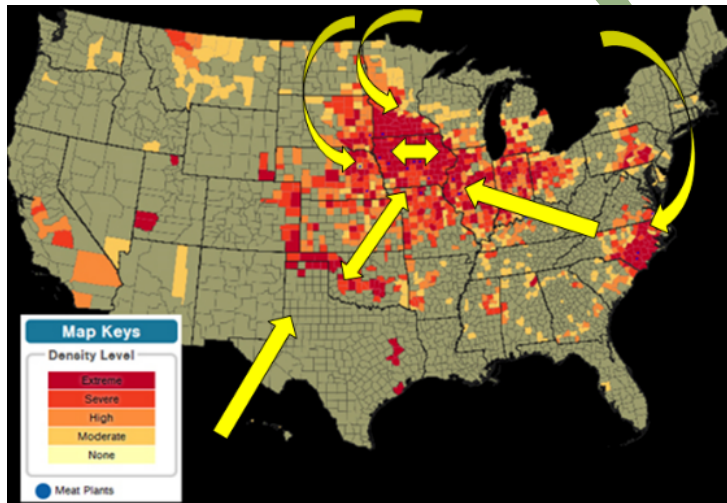
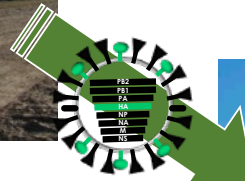
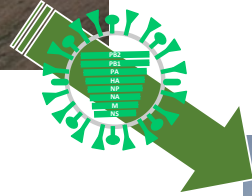
All in, All out by farrowing room – piglets weaned offsite



IAV moves with pig flows



IAV moves regionally with pig transport





Thanks, Canada!



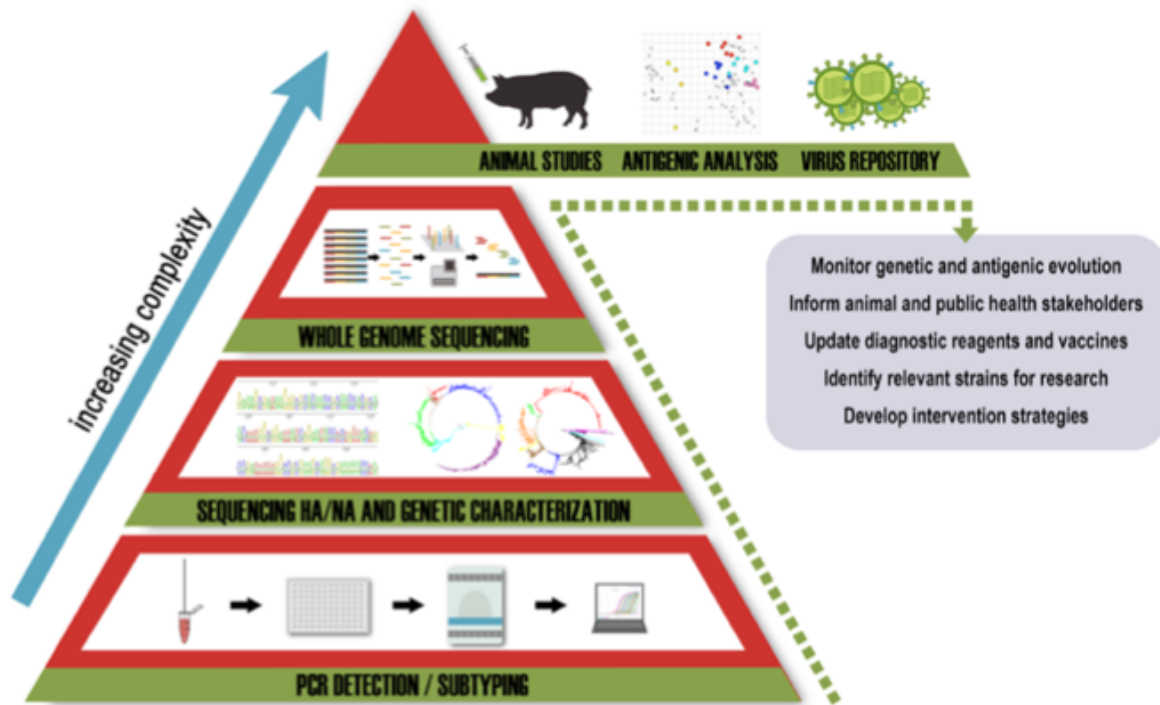
30 million pigs

imported into **Iowa** annually, along with the ~ 20 million that are born in Iowa. These are both weaned pigs and feeder pigs. Other corn belt states also receive pigs from within the U.S. and Canada, but Iowa is the **pig import mecca**. Some sites comingle sources.

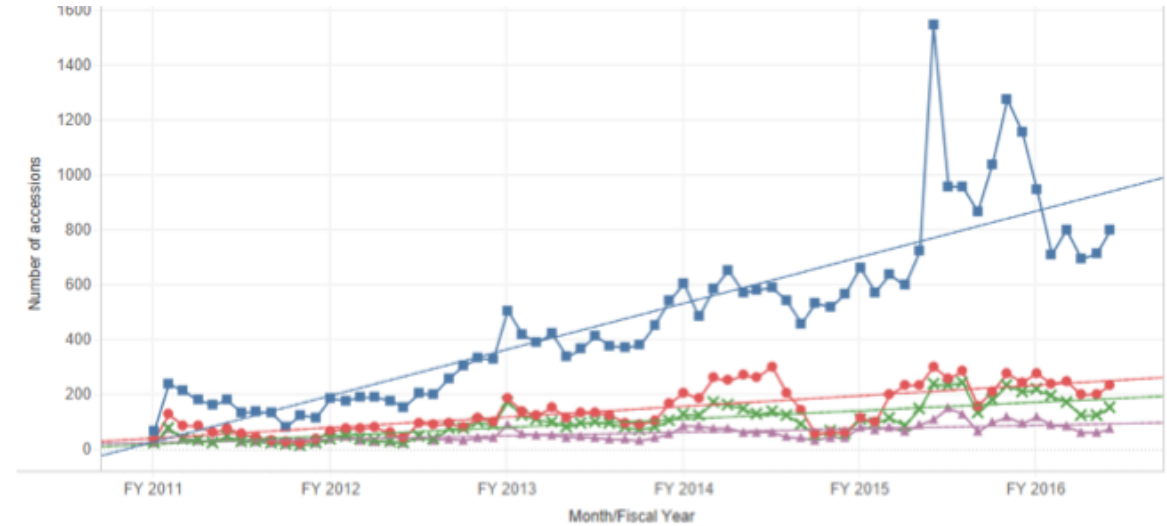


Surveillance for IAV in swine

How do we know what IAV are predominant in the U.S. swine population?

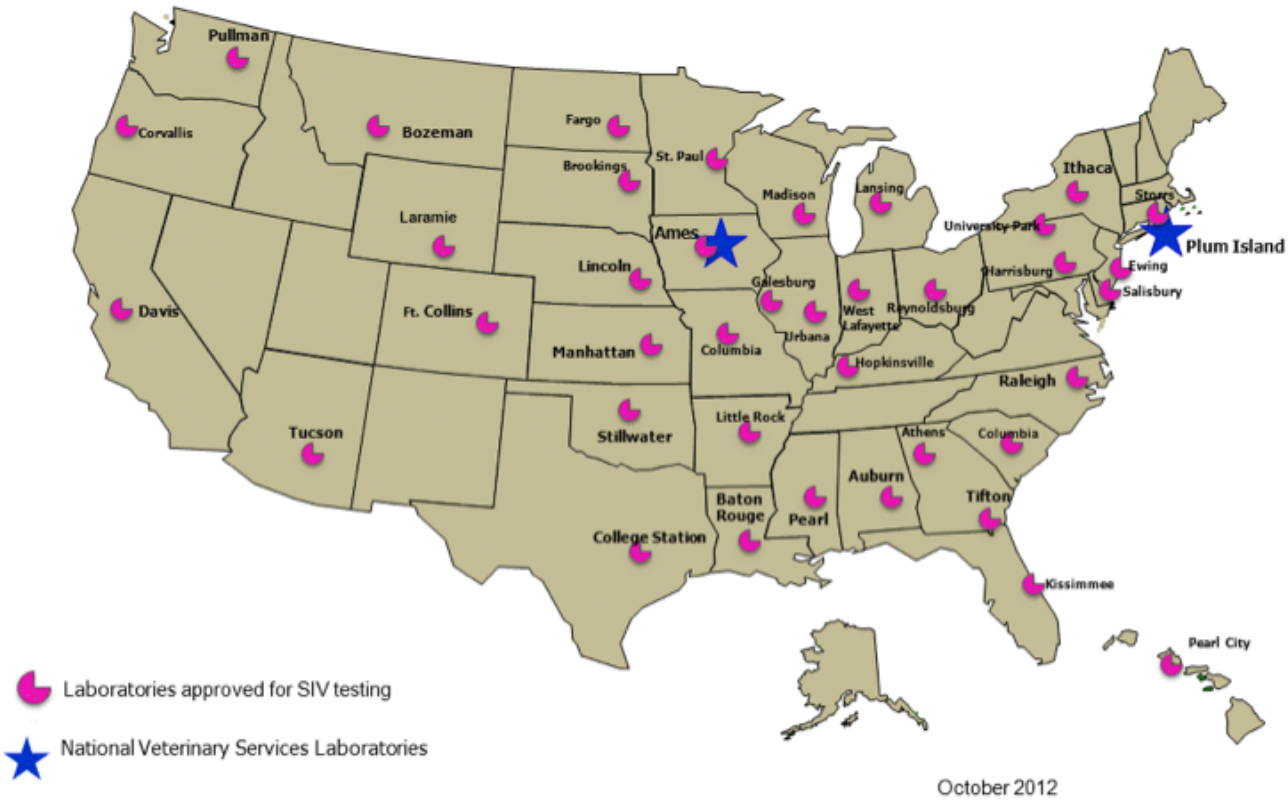


Surveillance Pyramid



- USDA Surveillance System active since 2009
- Virus isolates have HA and NA sequenced for all, WGS for subset
- Sequences in GenBank
 - A/swine/Arkansas/A01840698/2015
- Isolates available through USDA NVSL repository
 - http://www.aphis.usda.gov/library/forms/pdf/VS_Form4_9.pdf
 - Email your request to: NVSL_Userfee@aphis.usda.gov

USDA IAV Surveillance National Animal Health Laboratory Network



Swine Health Monitoring Surveillance

Last Modified: Apr 15, 2017



Influenza A Virus in Swine (IAV-S)

- Swine Influenza Surveillance Update (August 2012)
- Influenza Virus Surveillance in Swine - Program Overview for Veterinarians (AASV)
- Producer Guide to Influenza Virus Surveillance in Pigs (pdf)

Quarterly Surveillance Reports

FY2015: 1st Quarter / 2nd Quarter / 3rd Quarter / 4th Quarter
 FY2016: 1st Quarter / 2nd Quarter / 3rd Quarter / 4th Quarter

2015 IAV-S Surveillance Program Assessments

Internal and external program reviews were initiated in FY 2015 for APHIS' surveillance program for influenza A virus in swine (IAV-S) to assess the program and help inform future VS budget formulation efforts. The original funding for this program was received from DHHS as part of a fiscal year (FY) 2009 supplemental appropriation in response to the H1N1 pandemic. This funding source is projected to last through FY 2016. Funding beyond FY2016 is uncertain.

The assessment undertaken by APHIS' Office for Policy and Program Development (PPD) was meant to evaluate what results had been achieved by the IAV-S surveillance program and to determine changes that would be needed as the current program is transitioned into part of a larger comprehensive surveillance program for swine. It incorporates the opinions of key stakeholders and program officials to highlight issues that may be relevant to future program management or budget formulation activities. The external review, performed under contract with an independent scientific professional, examined the technical and scientific merit of the program and made recommendations for future program efficiencies.

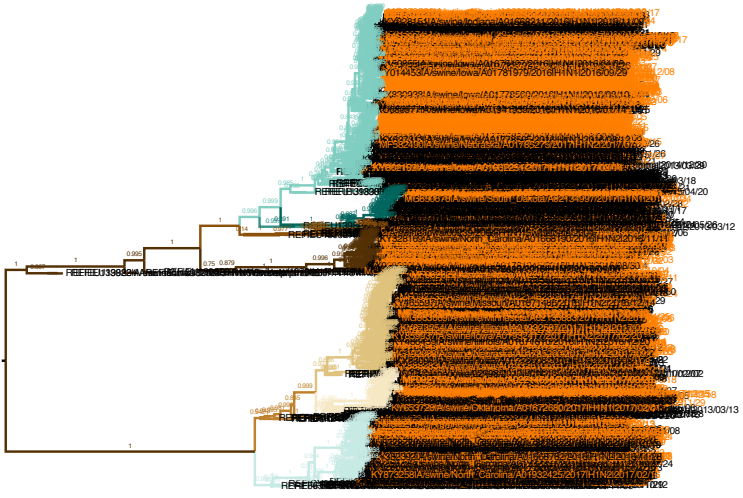
- IAV-S National Surveillance: APHIS-Policy and Program Assessment Executive Summary
- IAV-S National Surveillance Technical Review Executive Summary with Recommendations

https://www.aphis.usda.gov/aphis/ourfocus/animalhealth/animal-disease-information/swine-disease-information/ct_swine_health_monitoring_surveillance

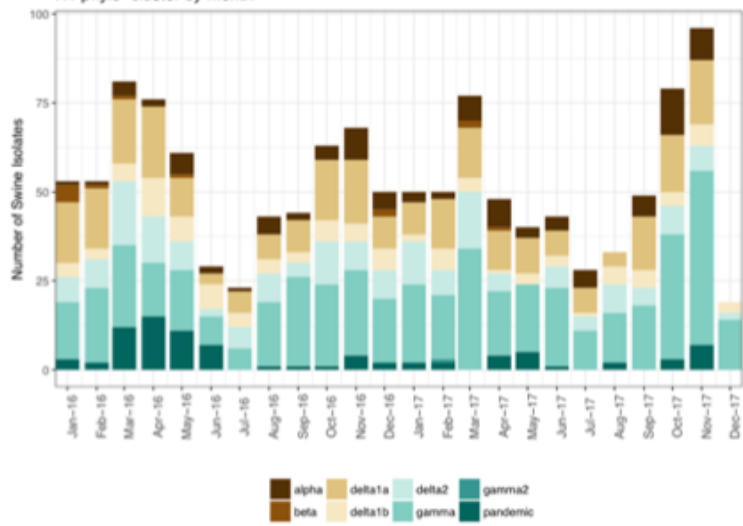
Started in 2009

Genetic Diversity of Swine H1 and H3 HA Genes

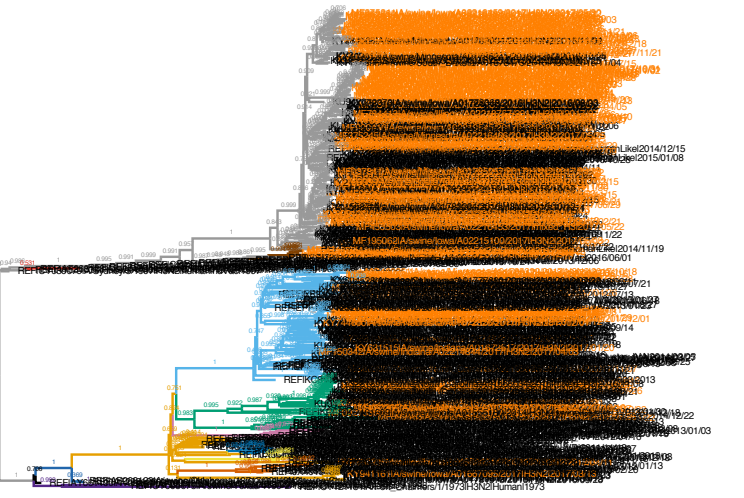
swine H1



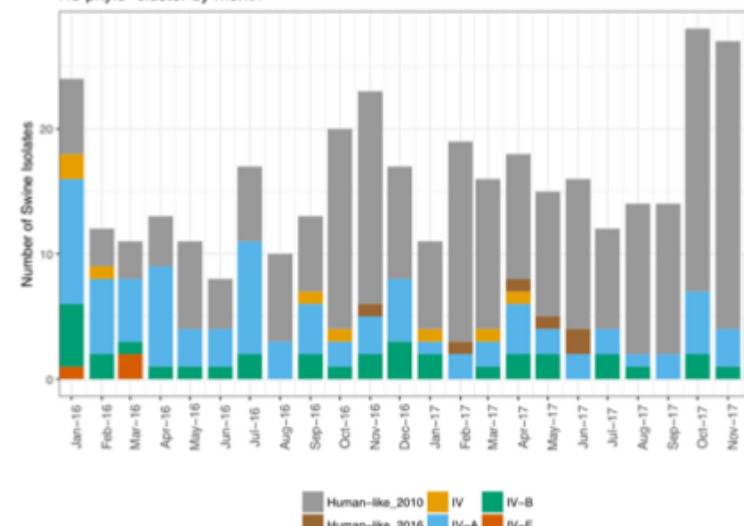
H1 phylo-cluster by month



swine H3



H3 phylo-cluster by month

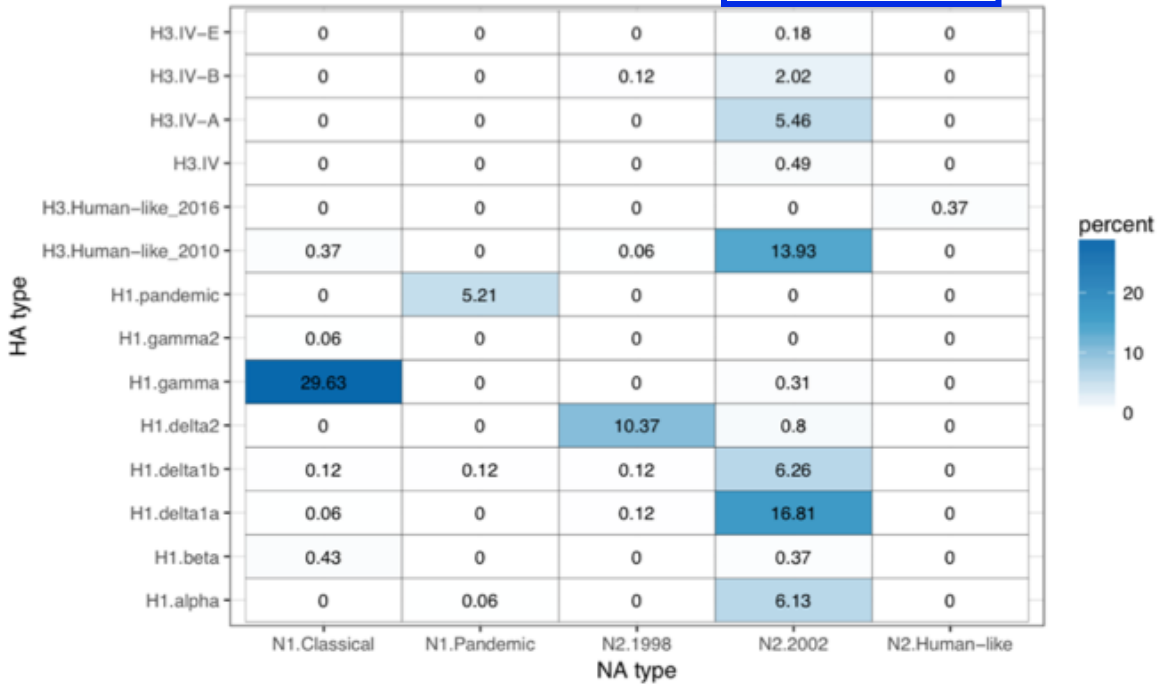


HA and NA Clade Combinations



Rolling 2 year window

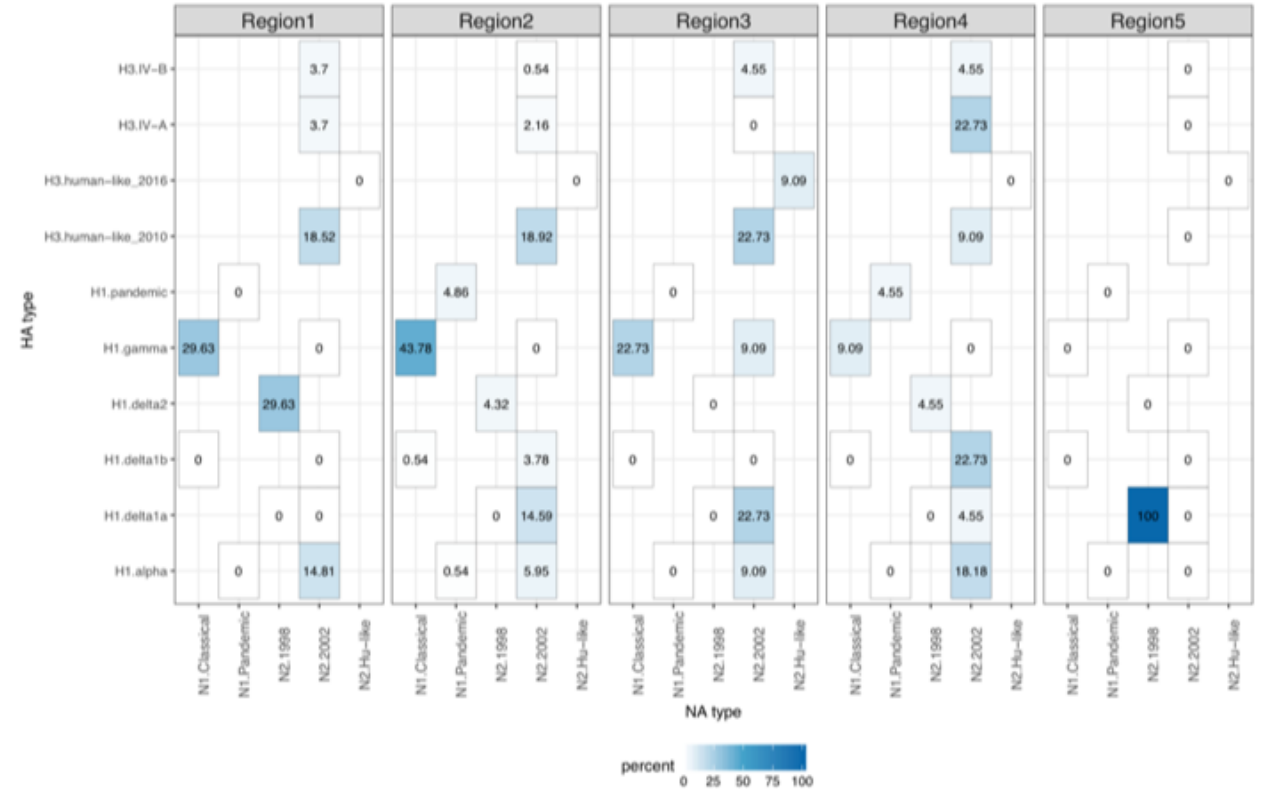
Percentage of HA and NA combinations – Jan 2016 to Dec 2017



Total HA & NA combinations – 1630

FY18 Quarter 1

Percentage of HA and NA combinations by Region



Total HA & NA combinations – 159

Genotype patterns

H1N1 and H1N2

PB2	PB1	PA	NP	M	NS	HA	NA	Total
T	T	P	P	P	T	γ	N1classic	77*
T	T	T	T	P	T	$\delta-1$	N2-2002	66*
T	T	T	P	P	T	$\delta-1$	N2-2002	59*
P	P	P	P	P	P	P	N1-P	51
T	T	T	T	P	T	γ	N1classic	40
T	T	T	T	T	T	γ	N1classic	40
T	T	T	T	T	T	$\delta-1$	N2-2002	37
T	T	T	P	P	T	γ	N1classic	25
T	T	T	T	T	T	β	N1classic	21
T	T	P	T	P	T	γ	N1classic	20
T	T	T	T	P	T	$\delta-2$	N2-1998	17
T	T	P	P	P	T	$\delta-1$	N2-2002	15
P	P	P	T	P	T	γ	N1classic	15
T	T	P	P	P	P	$\delta-1$	N2-2002	12
T	T	T	T	P	T	$\delta-2$	N2-2002	10

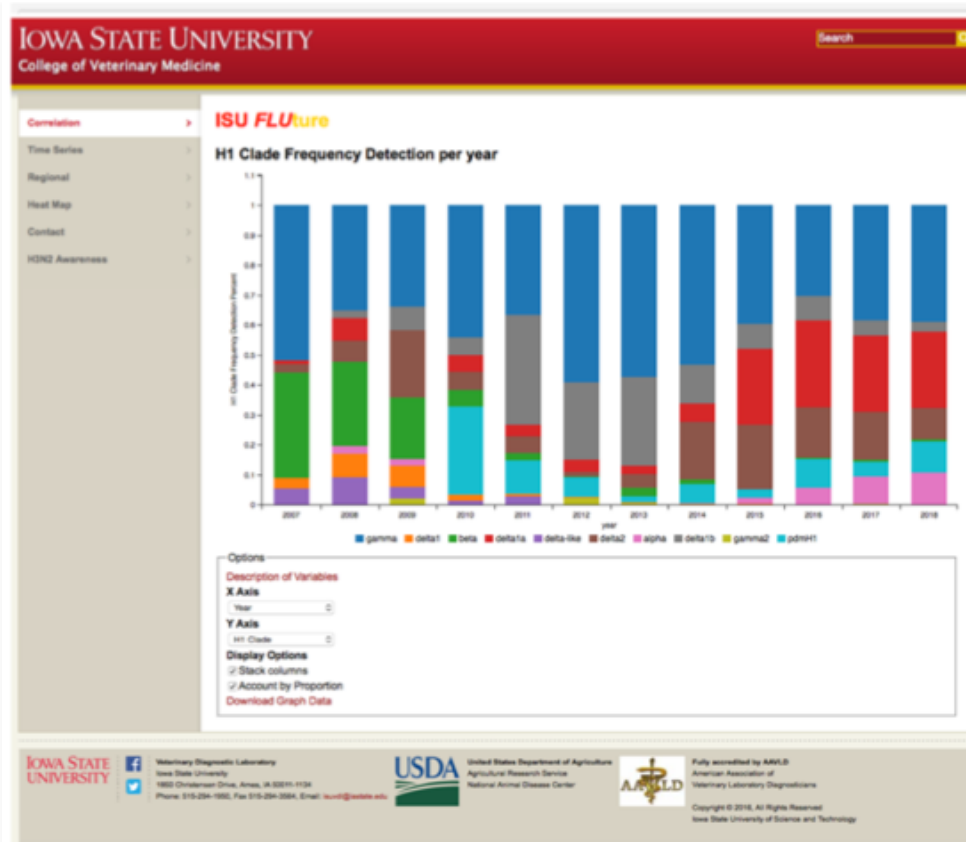
Gao et al., JGV 2017

H3N2

PB2	PB1	PA	HA	NP	NA	M	NS	Number of Isolates	2009	2010	2011	2012	2013	2014	2015	2016
Light Blue	Light Blue	Light Blue	Dark Blue	Light Blue	Purple	Red	Light Blue	119			22	61	23	8	4	1
Light Blue	Light Blue	Light Blue	Green	Light Blue	Purple	Light Blue	Light Blue	64	17	39	6	1	1			
Light Blue	Light Blue	Light Blue	Magenta	Light Blue	Purple	Light Blue	Light Blue	23	1	10	2	9	1			
Light Blue	Light Blue	Light Blue	Light Green	Red	Orange	Red	Red	22		2	14	6				
Light Blue	Light Blue	Light Blue	Dark Blue	Light Blue	Purple	Light Blue	Light Blue	19		12	5	2				
Light Blue	Light Blue	Red	Light Green	Red	Orange	Red	Red	15			5	10				
Light Blue	Light Blue	Light Blue	Grey	Light Blue	Purple	Red	Light Blue	10						4	6	
Light Blue	Red	Red	Yellow	Red	Purple	Red	Red	9			7	2				
Light Blue	Light Blue	Light Blue	Light Green	Red	Orange	Red	Light Blue	8			3	5				
Light Blue	Light Blue	Light Blue	Dark Blue	Red	Purple	Red	Light Blue	7				2	2	2	1	

Rajao et al., JVI 2017

Swine IAV web-based tools



IRD Influenza Research Database

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SEARCH DATA ANALYZE & VISUALIZE WORKBENCH SUBMIT DATA HELP

Home > Swine H1 Clade Classification

Swine H1 Clade Classification Tool

The swine H1 clade classification tool classifies the clade of the HA/H1 viruses from any host and for any NA subtype, with reference to the global swine H1 clade scheme (Anderson et al., 2016) the US swine H1 classification scheme. This tool infers the clade for a query sequence from its position within the reference tree. It is a collaboration between Catherine Macken at IRD and Tavis Anderson and others at the USDA.

- SOP for global swine H1 clade classification
- Global Swine H1 Clade Classification Reference Tree
- Global Swine H1 Clade Classification Reference Sequences
- SOP for US swine H1 clade classification
- US Swine H1 Clade Classification Reference Tree
- Description of US clades with name that include "like"

Sequences from other serotypes of HA, or other segments will yield unpredictable and likely incorrect results. If unsure of your sequence's segment or serotype, we suggest you use the IRD Sequence Annotation Tool (Analyze & Visualize > Annotate Nucleotide Sequences).

ANALYSIS NAME

INPUT SEQUENCES

- Analyze my custom sequences only.
Upload a file containing my sequences in FASTA format.
- Paste sequences in FASTA format.
- Analyze my custom sequences and associated metadata with IRD sequences.

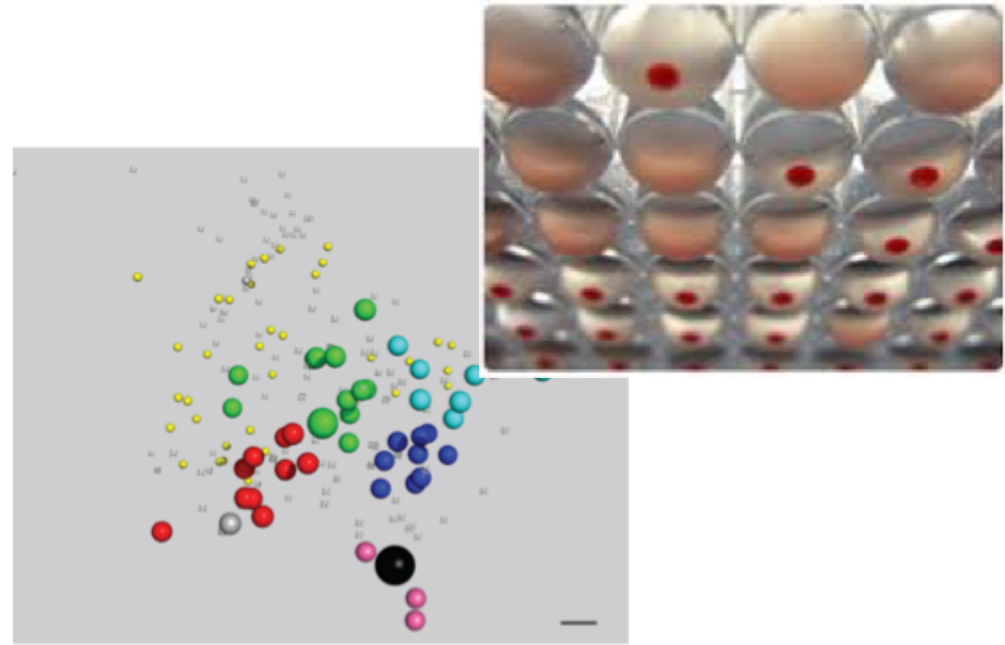
[Clear](#) [Run](#)

Release Date: Mar 8, 2018

This system is provided for authorized users only. Anyone using this system expressly consents to monitoring while using the system. Improper use of this system may be referred to law.

Influenza.cvm.iastate.edu
Michael Zeller

Fludb.org
Tavis Anderson

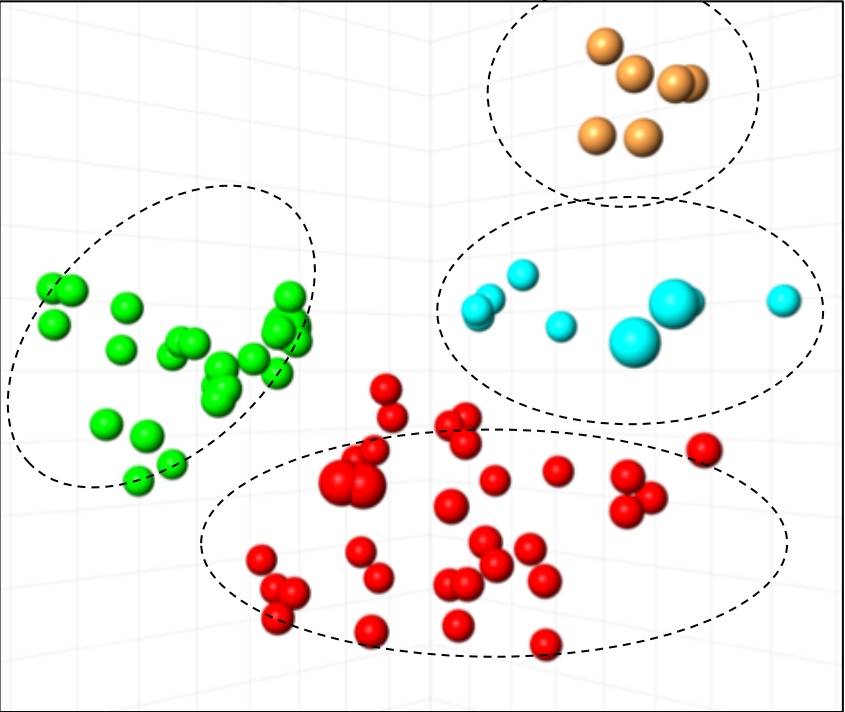


- Monovalent swine antisera
- Pairwise hemagglutination inhibition (HI) assays
- Collaboration with Nicola Lewis @ University of Cambridge

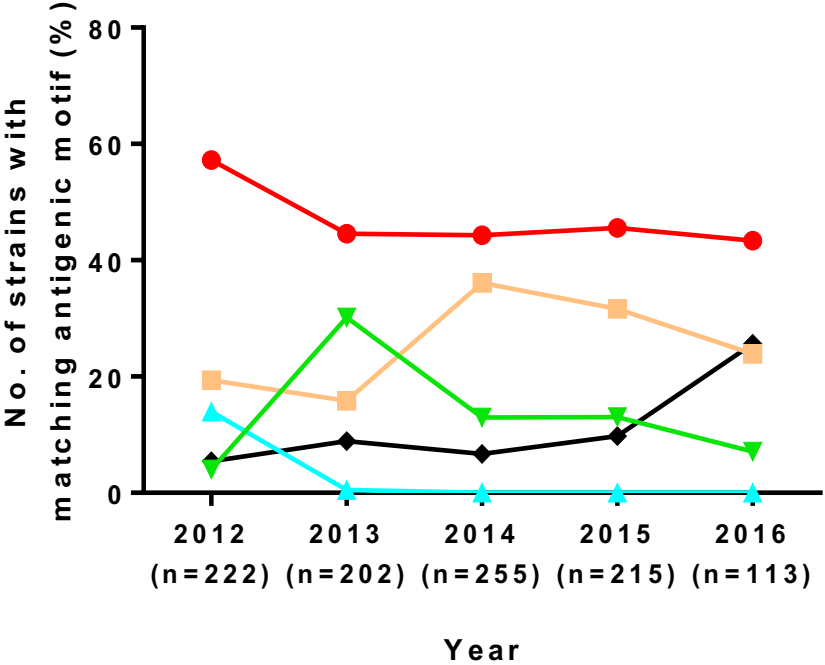
Antigenic Diversity of **IAV in Swine**

Cluster-IV H3 IAV in swine at the antigenic level

Strains characterized in the lab (cross-HI's with a established, representative panel)

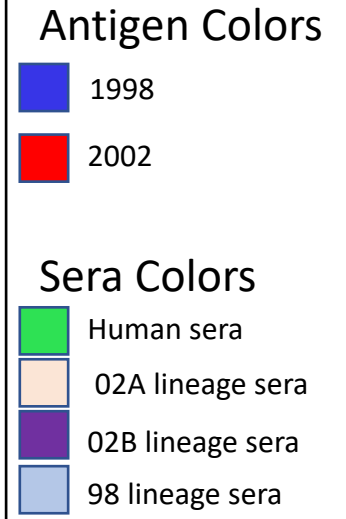
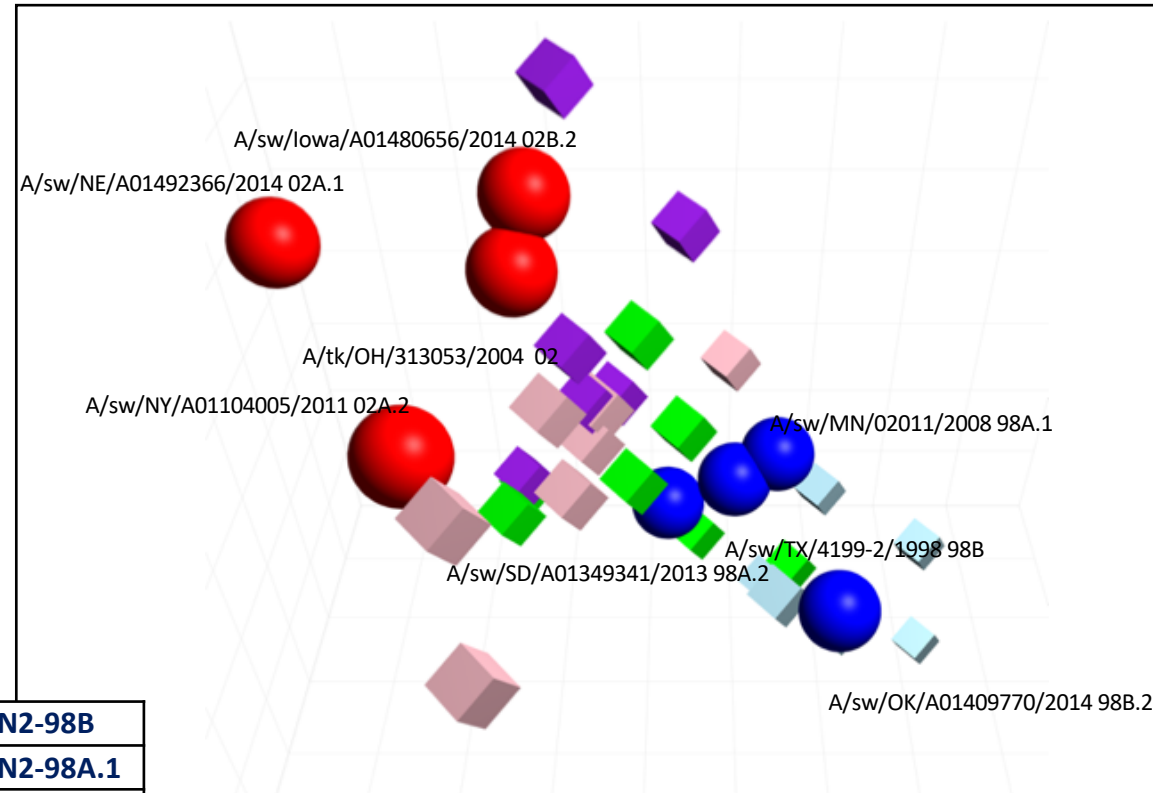
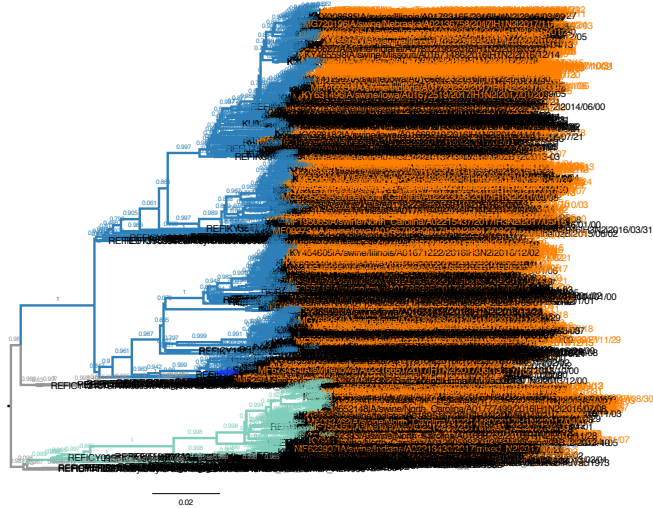


Inferred antigenic phenotypes over time



Lewis et al. J. Virol 2014
Unpublished data, M. Bolton & E. Abente

N2 mapping by NI - H9N2 antigens



rg-7:1(A/Swine/Texas/4199-2/1998)	H9N2-98B
rg-att7:1(A/Swine/Minnesota/02011/2008)	H9N2-98A.1
rg-att7:1(A/Swine/South Dakota/A01349341/2013)	H9N2-98A.2
rg-att7:1(A/swine/Oklahoma/A01409770/2014)	H9N2-98B.2
rg-att7:1(A/TURKEY/OHIO/313053/2004)	H9N2-02
rg-att7:1(A/Swine/Nebraska/A01492366/2014)	H9N2-02A.1
rg-att7:1(A/Swine/New York/A01104005/2011)	H9N2-02A.2
rg-att7:1(A/Swine/Iowa/A01480656/2014)	H9N2-02B.2

Bryan Kaplan
with Daniel Perez & Jeff Santos @ UGA

Variant IAV

- When a swine-lineage IAV is detected in humans, it is called “**variant**” to distinguish it from human seasonal and avian lineages (e.g. H3N2v).
- Non-seasonal detections became reportable to WHO in 2005.
- Since 2005, the CDC developed PCR tests implemented in public health labs to differentiate variant IAV from seasonal IAV and created a Zoonotic Virus Team.
 - 468 total variant detections of all subtypes
 - 309 variants were H3N2v detected in 2012
- Variants tend to be dead end with limited human to human transmission.
- CDC routinely checks cross-reactivity of variants against ferret anti-sera to seasonal vaccine strains and human population sera.
 - Children born after 2001 have limited immunity to H3N2v.
- The CDC presents this data at the WHO vaccine consultation meetings.
 - ~8 variants from the US selected as pandemic preparedness candidate vaccine viruses (along with Eurasian swine H1N1 and several avian influenza strains).



The Fair Connection

TAKE ACTION to Prevent the Spread of Flu Between Pigs and People

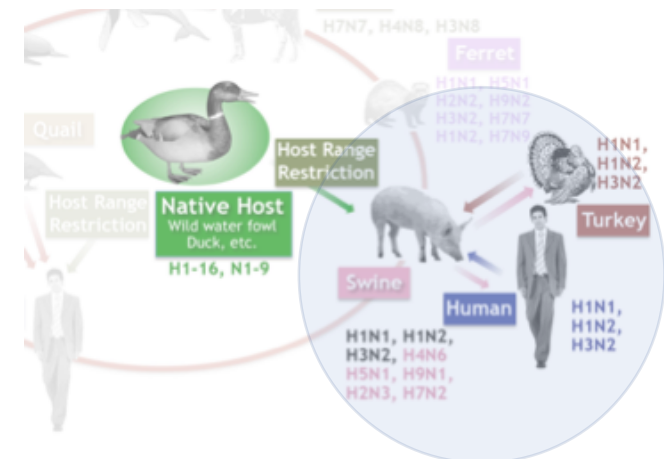


Background

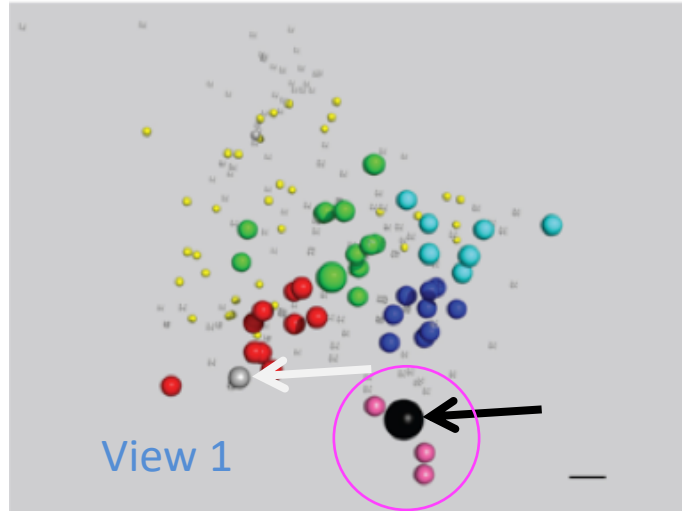
Pigs can be infected with their own influenza viruses (called swine influenza) that are usually different from human flu viruses. While rare, influenza can spread from pigs to people and from people to pigs. When people get swine flu viruses, it's usually after contact with pigs. This has happened in different settings, including fairs. The Centers for Disease Control and Prevention (CDC) recommends people take the following actions to help prevent the spread of flu between pigs and people.

CDC Recommendations for People with High Risk Factors:

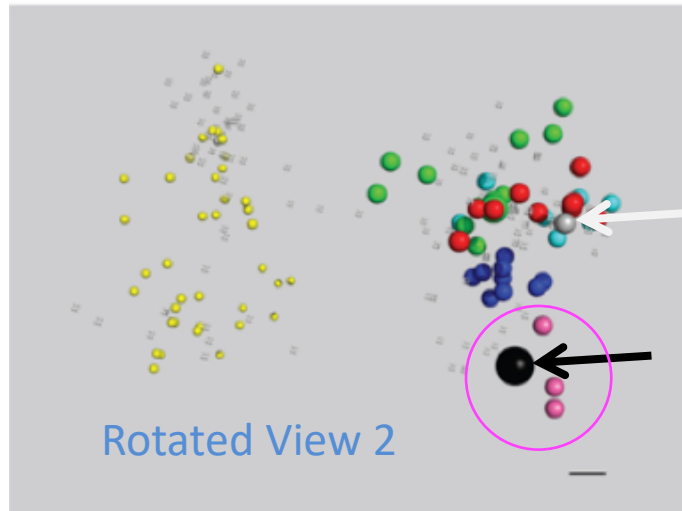
- Since 2011, the majority of human variant cases have been associated with agricultural exhibits (county and state fairs).
- The IAV detected in show pigs are similar to those found in USDA surveillance.
- Outbreaks in show pigs tend to coincide with influenza-like illness in the stockman (adolescents and teens) or attendees.



Swine-human antigenic analysis



View 1



Rotated View 2

Key:

Alpha

Beta

Gamma (large sphere = A(H1N1)/swine/Minnesota/A01567490/2014)

PDM (Grey = A/California/04/2009)

Small yellow = delta lineage (Grey=A/Michigan/02/2003)

Pink = 2015 gamma lineage in pigs

Black = A/Ohio9/2015

Scale bar = 1AU or a two-fold difference in HI assay titre

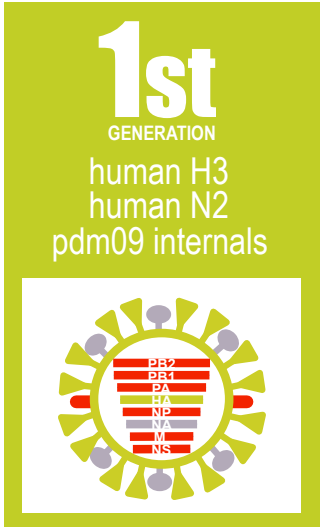
Virus 1	Virus 2	AU Distance
A(H1N1)/CALIFORNIA/4/2009 MDCK4-AG	A(H1N1)/SWINE/NORTH CAROLINA/A02076926/2015 MDCK2-AG	3.4
A(H1N1)/CALIFORNIA/4/2009 MDCK4-AG	A(H1N1)/SWINE/NORTH CAROLINA/A01841602/2015 MDCK2-AG	4.9
A(H1N1)/CALIFORNIA/4/2009 MDCK4-AG	A(H1N1)/SWINE/OHIO/A01847657/2015 MDCK2-AG	5.1
A(H1N1)/CALIFORNIA/4/2009 MDCK4-AG	A/OHIO/9/2015 MDCK2-AG	4.7
A(H1N1)/MEXICO/4108/2009 MDCK3-AG	A(H1N1)/SWINE/NORTH CAROLINA/A02076926/2015 MDCK2-AG	3.3
A(H1N1)/MEXICO/4108/2009 MDCK3-AG	A(H1N1)/SWINE/NORTH CAROLINA/A01841602/2015 MDCK2-AG	4.9
A(H1N1)/MEXICO/4108/2009 MDCK3-AG	A(H1N1)/SWINE/OHIO/A01847657/2015 MDCK2-AG	5.2
A(H1N1)/MEXICO/4108/2009 MDCK3-AG	A/OHIO/9/2015 MDCK2-AG	4.4

2015 swine gamma similar to A/Ohio/9/2015 (155E, 169R, 222G)

- A/swine/North_Carolina/A02076926/2015 H1N1-gamma (155G, 169K, 222D)
- A/swine/North_Carolina/A01841602/2015 H1N1-gamma (155E, 169K, 222D)
- A/swine/Ohio/A01847657/2015 H1N1-gamma (155E, 169R, 222D)

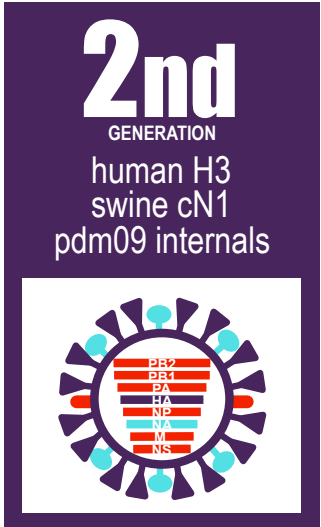
Gamma H1N1v

Human seasonal H3N2 introduction into swine



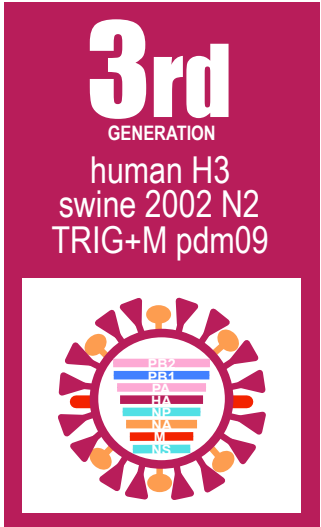
2012

H3N2



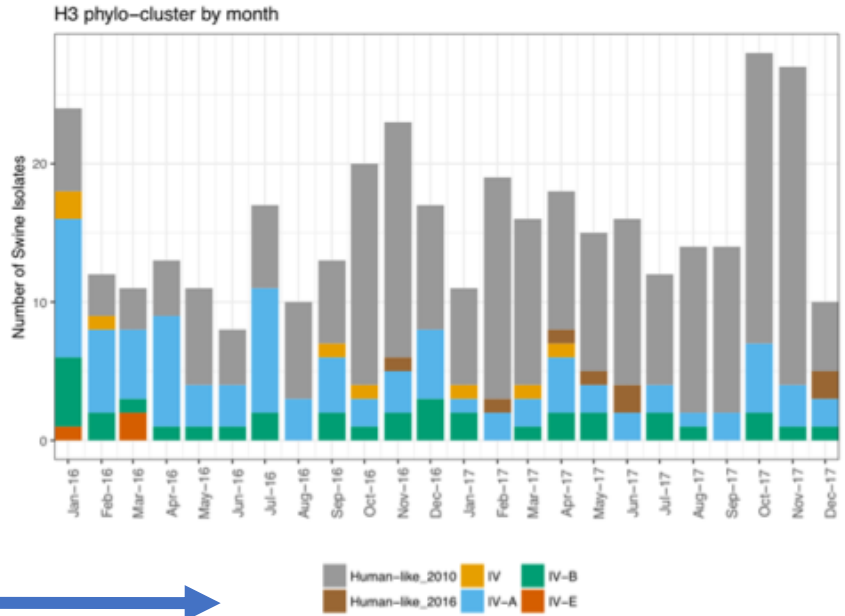
2013-14

H3N1



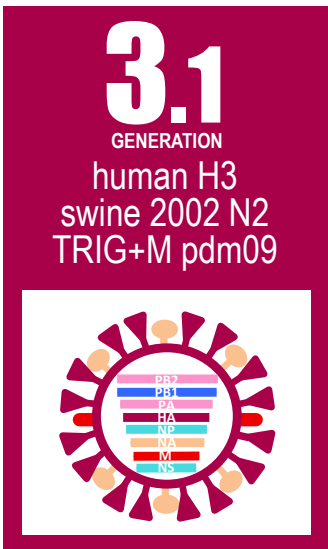
2014-current

H3N2



The 3rd genotype of human-like H3N2 has been the predominant H3 detected in the USDA swine surveillance system since 2014. **This genotype also infected 16 humans in close contact with swine at fair exhibits in the summer of 2016.**

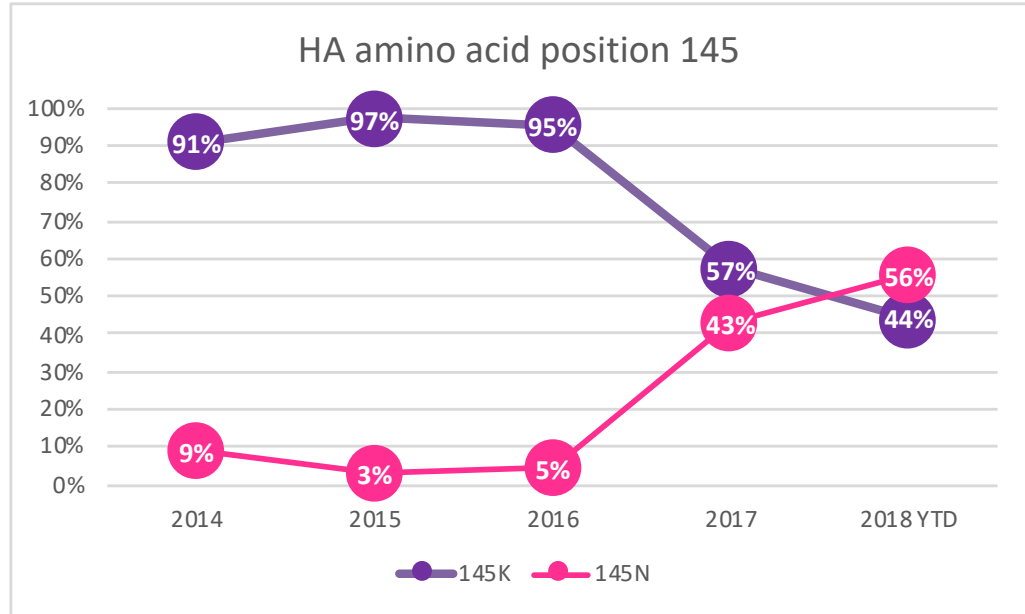
Genetic and antigenic evolution of the 2010 hu-like H3N2 in swine 2017



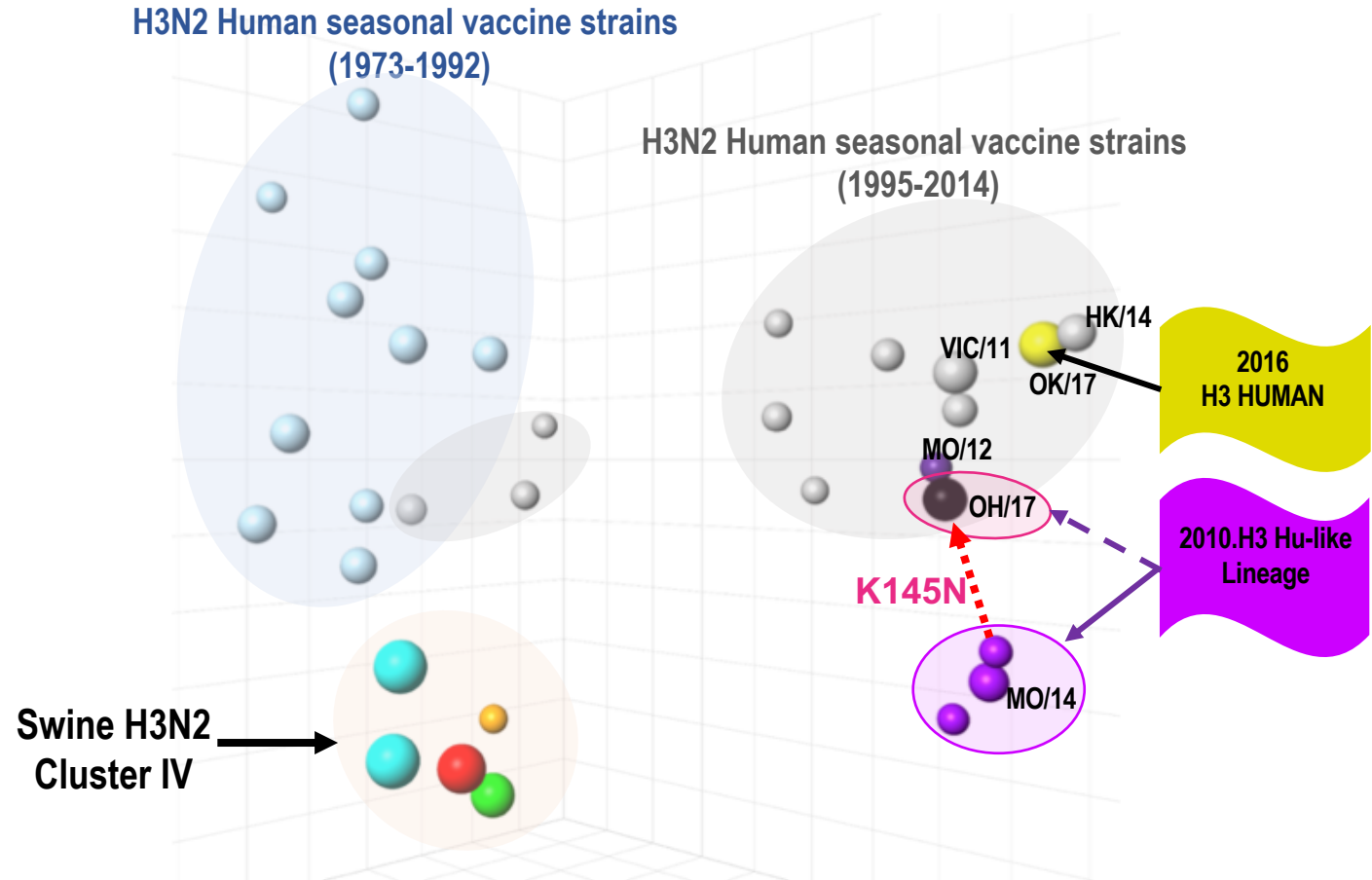
• Generation 3.1

- Switched N2 clade from N2-02A to N2-02B.
- Amino acid changes in HA, position 145 previously shown to be a dominant antigenic site (**K145N**).
- Genome constellation: TTTTPT
 - PB2, PB1, PA, NP, & NS from North American swine TRIG lineage
 - M from H1N1pdm09 lineage
- 62 human variant cases in 2017, nearly identical viruses.
 - Mostly county fairs in Ohio, Michigan, and Maryland + others
 - Iowa case in a swine farm worker

Antigenic drift of 2017 H3N2 **K145N** in swine



Michael Zeller



Carine Souza

INFLUENZA CONTROL is not so simple...

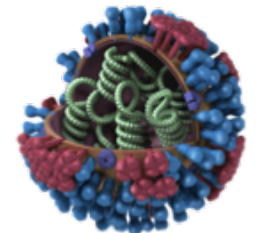
Especially if you are a pig.

- Interspecies transmission between humans and pigs continues to occur.
- Human IAV dramatically impacts the genetic expansion of IAV in swine, particularly the H1N1pdm09.
- Vaccines against influenza constantly need updating and not as easy as it seems to make a good vaccine.
- Pig movement adds to the complexity of IAV in swine.
- **What have we gained since the 1918 Spanish Flu Pandemic?**



Pandemic preparedness by WHO & CDC

- CDC Zoonotic Virus Team dedicated to this area of IAV and working groups with USDA, state animal health, and public health, and many international partners.
- Diagnostic assays at public health labs to detect non-seasonal IAV in human specimen.
- Awareness of influenza like illness off-season and associated with swine contact by physicians and local health departments.
- Sequence and antigenic analysis of animal IAV provides baseline knowledge needed for public health.
 - HI tests with monovalent ferret anti-sera and human population sera for novel IAV detections in humans.
- Moving beyond the simple focus of HA in inactivated vaccines and pairwise HI assays for human vaccine concepts.
 - Prior exposure history, repeated vaccination, NA and other viral targets...
- Vaccine seed strains made and held in reserve.
- **Not just swine, but avian, canine, equine...**



Future Opportunities in Swine IAV



- Surveillance data revealing patterns from which to draw vaccine strain decisions for swine and to inform public health.
- Changes in USA vaccine licensing regulations.
- New vaccine platforms and technology – RNA RP vector & LAIV
 - Rapid change of HA and NA (Vectored>WIV & LAIV)
 - Broader cross-protection (LAIV>RP>WIV)
 - Improved mucosal immunity (LAIV>RP & WIV)
- New computational tools to enhance surveillance and HI data analysis
 - Allows a better understanding of antigenic consequence of changes in the HA.
- Repeatable swine models for VAERD and antigenic imprinting.
- Stronger relationships with CDC, other influenza host sectors, and international networks.

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