Influenza Surveillance and Vaccine Effectiveness in the DoD 2011 – 2012

Armed Forces Health Surveillance Center (AFHSC)

Naval Health Research Center (NHRC)

United States Air Force School of Aerospace Medicine (USAFSAM)

DoD Global Influenza Network Partners

Presentation to the Vaccines and Related Biological Products Advisory Committee (VRBPAC) - 28 February 2012

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****Representing the DoD CONUS and OCONUS lab-based influenza surveillance activities**

Disclaimer

The views expressed in this presentation are those of the author and do not reflect the official policy or position of the Department of Defense or the U.S. Government

Briefing Outline

PURPOSE: Provide a concise update to the VRBPAC on DoD influenza surveillance activities, 2010-2011

1. Strain Circulation
2. Molecular Analyses
3. Vaccine Effectiveness
4. Serology

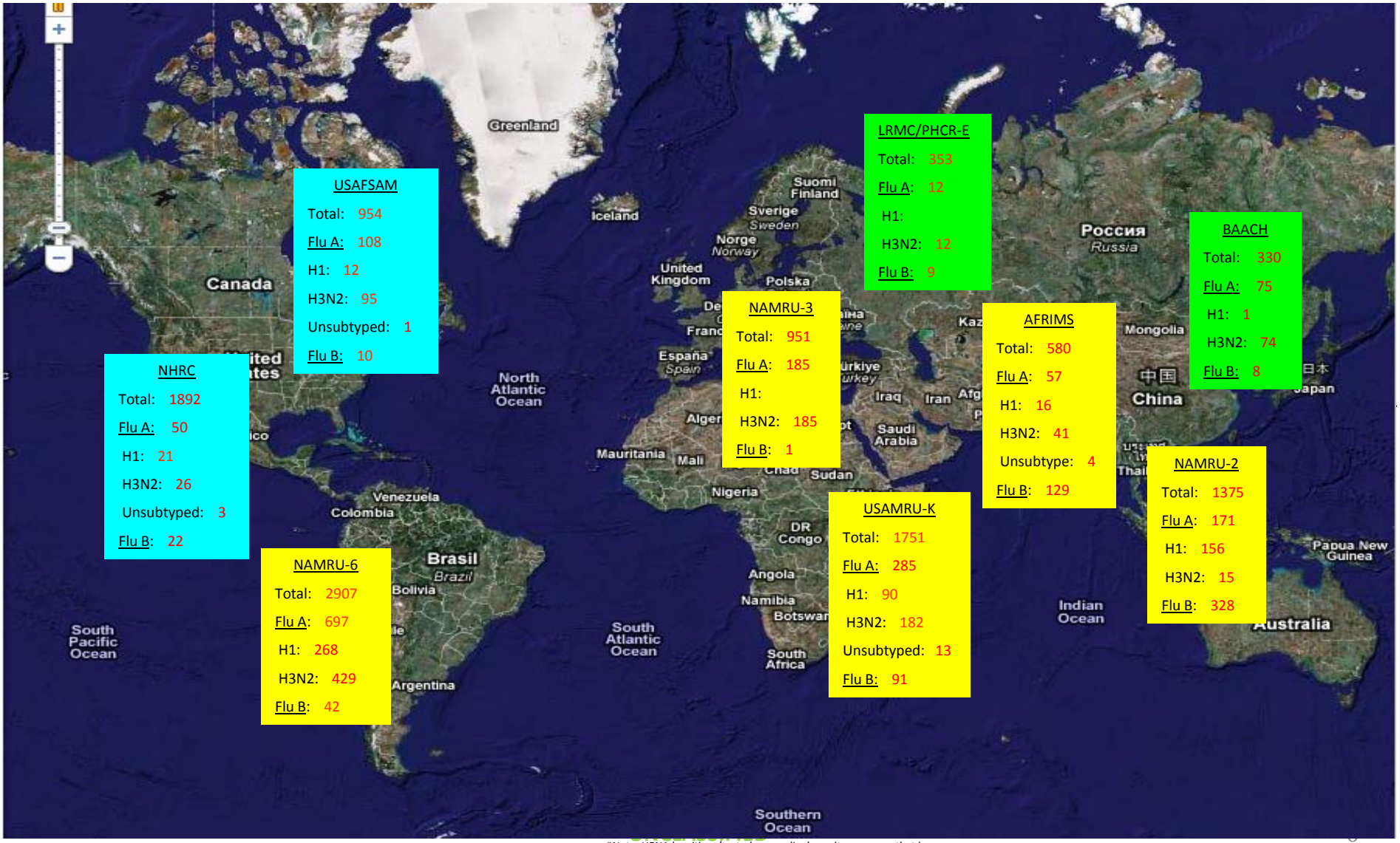
Breadth of DoD Influenza Surveillance

- Global Virus Surveillance
  - Approximately 500 locations in over 70 countries globally
    - Military; Local government/academic
  - Extensive characterization capabilities within the DoD
    - Culture, HAI, PCR (battery), Sequencing
  - Rapid sharing of results with CDC and/or regional WHO reference centers
    - More than 38,000 samples collected and analyzed in fiscal year 2011
    - Published over 400 sequences to GenBank in fiscal year 2011
- Comprehensive Epidemiology and Analysis Capabilities
  - 1.4 Million Active Duty records (health care utilization, immunizations, deployment, reportable diseases, etc)
    - 12 data feeds into DMSS, additional in house
    - Medical Surveillance Monthly Reports, Ad-hoc requests, Studies/analyses, Routine reports/summaries
    - Weekly influenza reports
    - Vaccine safety and effectiveness studies


USAMRIID
GEIS
AFIP
WRAIR-DVD
NMCPHC
Equator
Equator
AFRIMS
U_IOWA
CHPPM-S
LRMC
NAMRU-2
NAMRU-3
NHRC
NMRCD-Lima
USAFSAM
USAMRU-K
18thMEDCOM
WRAIR-DVD
NHRC Ships

Global Influenza Activity Report

Specimens Received & Tested: Total= *Cumulative Reports since EpiWeeks 39/40*



USAFSAM
Total: 954
Flu A: 108
H1: 12
H3N2: 95
Unsubtyped: 1
Flu B: 10

NHRC
Total: 1892
Flu A: 50
H1: 21
H3N2: 26
Unsubtyped: 3
Flu B: 22

NAMRU-6
Total: 2907
Flu A: 697
H1: 268
H3N2: 429
Flu B: 42

LRMC/PHCR-E
Total: 353
Flu A: 12
H1:
H3N2: 12
Flu B: 9

NAMRU-3
Total: 951
Flu A: 185
H1:
H3N2: 185
Flu B: 1

AFRIMS
Total: 580
Flu A: 57
H1: 16
H3N2: 41
Unsubtype: 4
Flu B: 129

BAACH
Total: 330
Flu A: 75
H1: 1
H3N2: 74
Flu B: 8

USAMRU-K
Total: 1751
Flu A: 285
H1: 90
H3N2: 182
Unsubtyped: 13
Flu B: 91

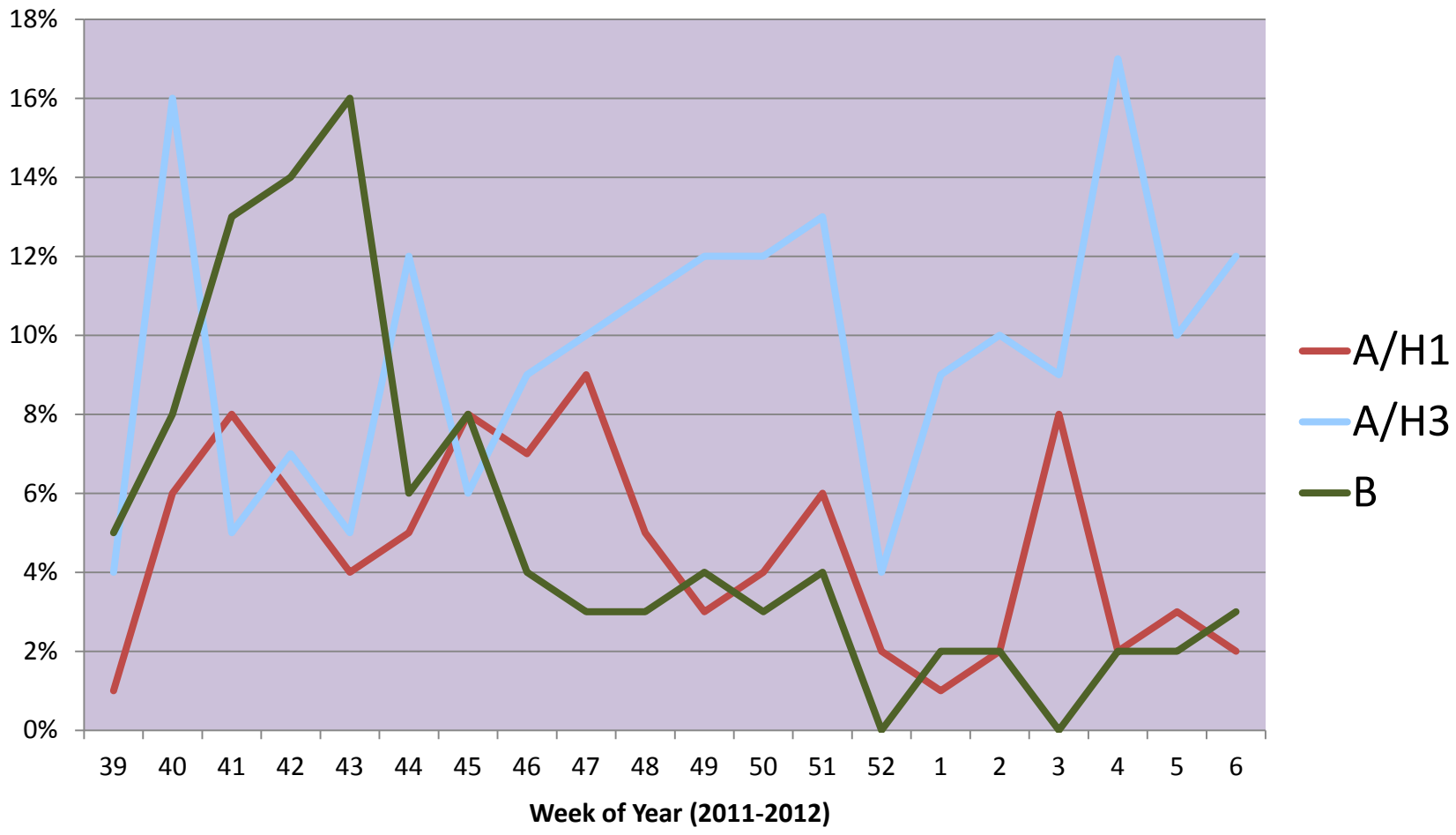
NAMRU-2
Total: 1375
Flu A: 171
H1: 156
H3N2: 15
Flu B: 328

DoD Service Hubs | Medical Centers | DoD Research Labs

üNote: H5N1 (positives/tested or pending) results are cases that have been confirmed and reported through WHO in compliance with the International Health Regulations 2005.

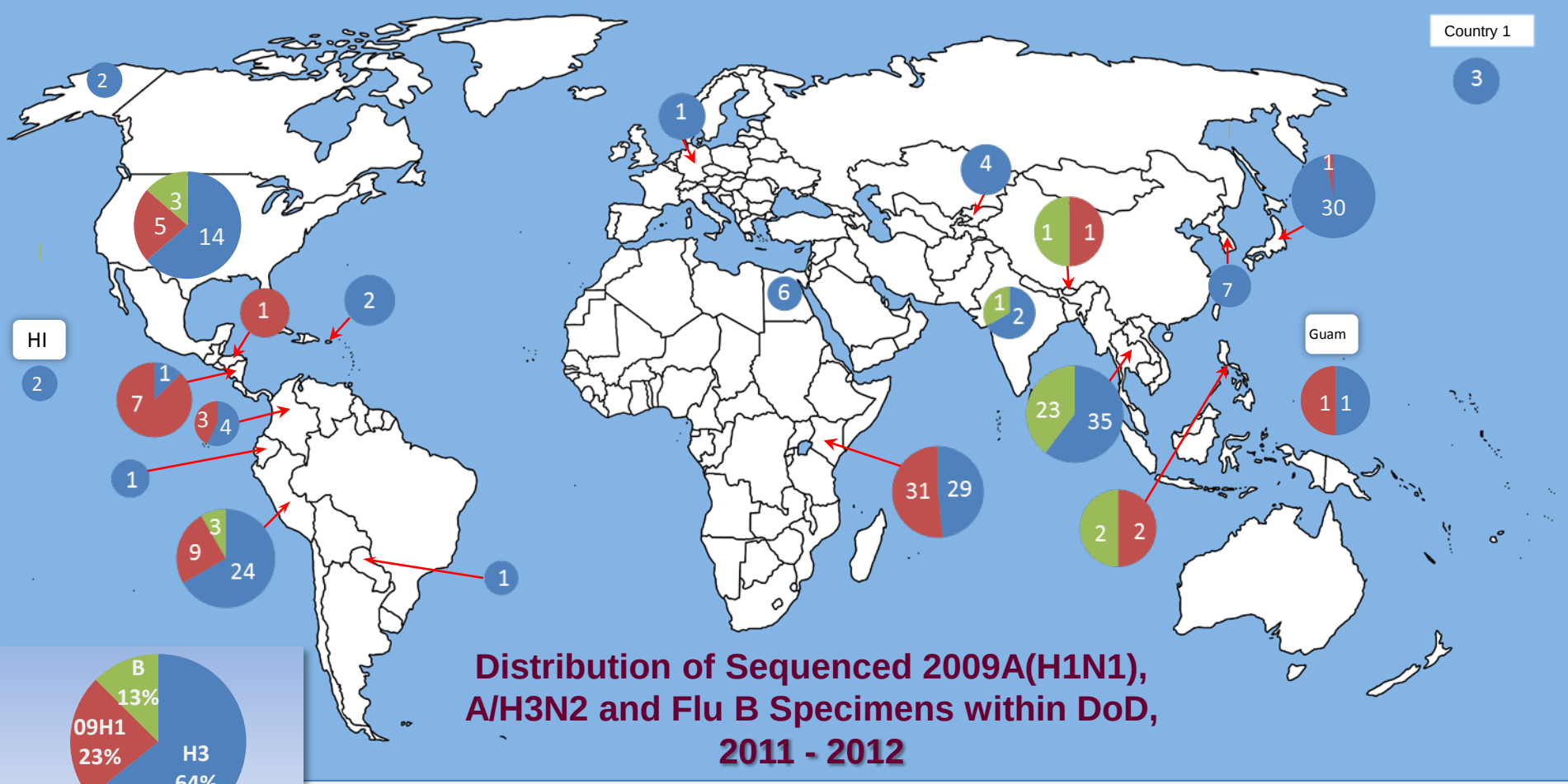
February 2012

DoD Global Strain Trends



Summary of Circulating Strain Activity

- Little regional difference in virus circulation
  - Predominately H3 across all regions with the exception of B in Southeast Asia
- Overall influenza activity is low to moderate this season
- Recent increased percentage of influenza positive specimens among military beneficiaries
  - Recruits & Shipboard: co-circulation of A/H3 & B
  - Dependents and other Active Duty: predominately A/H3



Distribution of Sequenced 2009A(H1N1), A/H3N2 and Flu B Specimens within DoD, 2011 - 2012

% of Total Sequenced

Contributors

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Armed Forces Research Institute of Medical Science – Bangkok, Thailand
Naval Medical Research Unit 3 – Cairo, Egypt
Naval Medical Research Unit 6 – Lima, Peru
U.S. Army Medical Research Unit – Nairobi, Kenya
U.S. Army Medical Centers in CONUS and OCONUS

LOCATIONS

Bhutan
Colombia
Country 1
Ecuador
Egypt
Germany
Honduras
India
Japan
Kenya
Korea
Kyrgyzstan
Nicaragua
Paraguay
Peru
Philippines
Thailand
United States (including Guam & Puerto Rico)

United States Air Force School of Aerospace Medicine

Influenza A/09(H1N1) HA (HA1) Phylogenetic Analysis 2011 -2012

- Sequenced strains exhibited protein homology of 96.3% - 98.7%
- 88% of specimens collected prior to December 2011
- All sequenced possess change, E374K, correlating with monoclonal antibody inhibition in certain IFA testing kits.
- Two main groups, both possessing D97N (aspartic acid to asparagine).
  - Smaller group defined by two mutations, R205K (arginine to lysine) and V249L (valine to leucine). This group is mostly older and Kenyan strains.
  - Larger group is defined by S185T (serine to threonine) and splits into two subgroups. The smaller but more recent group possesses A197T (alanine to threonine) and includes almost all of our recent A/09H1N1 strains

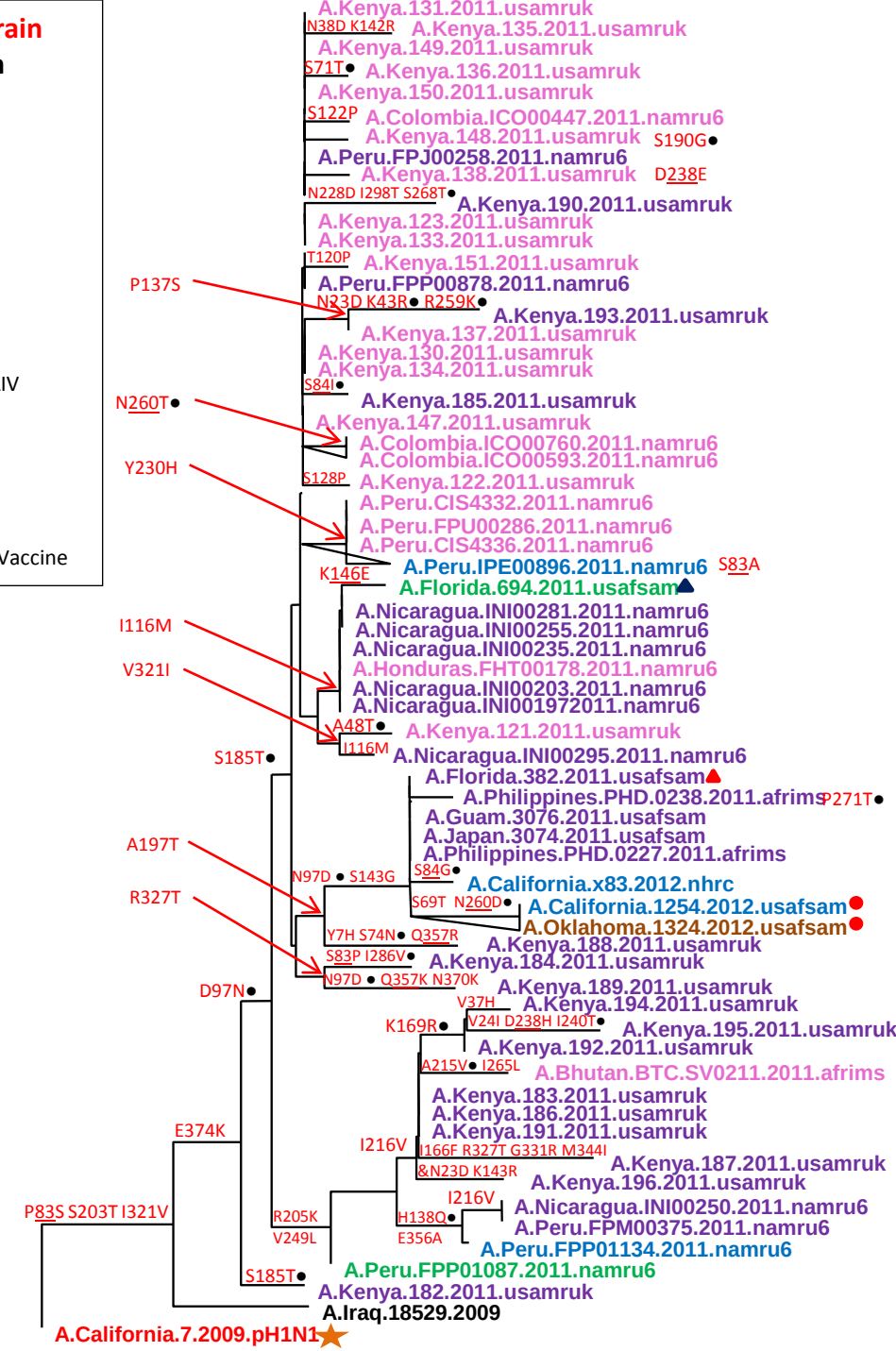
Source: USAFSAM/PHE (2510 5th Street, Wright-Patterson Air Force Base, OH 45433)

09H1N1 Vaccine strain
Reference Strain

N=61

May-Aug 2011	39%
Sep-Nov 2011	49%
Dec 2011	3%
Jan 2012	7%
Feb 2012	2%

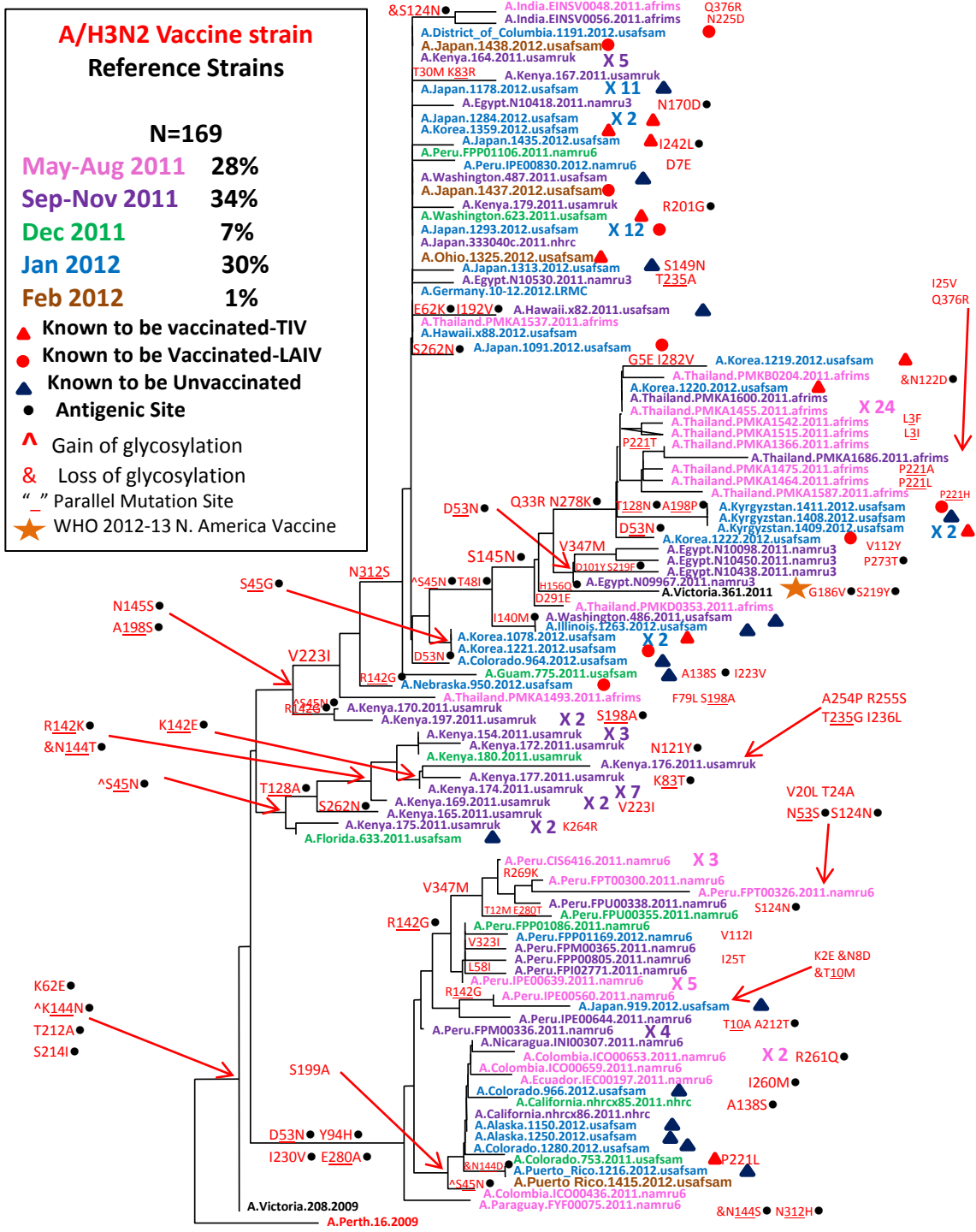
▲ Known to be vaccinated-TIV
● Known to be Vaccinated-LAIV
▲ Known to be Unvaccinated
^ Gain of glycosylation
& Loss of glycosylation
Antigenic Site
"_" Parallel Mutation Site
★ WHO 2012-13 N. America Vaccine



Influenza A/H3N2 HA (HA1) Phylogenetic Analysis 2011-2012

- Sequenced strains exhibited protein homology of 96.5%-99.4%
- 33 specimens from patients known to be previously vaccinated (18 LAIV, 15 TIV).
- All sequenced specimens characterize into A/Victoria/208/2009-like subgroup, both contain four mutations at antigenic sites, K62E (lysine to glutamic acid), K144N (lysine to asparagine) creating a glycosylation motif, T212A (threonine to alanine) and S214T (serine to threonine). Three main groups split from this node.
  - Smaller group of Kenyan strains containing two additional mutations T128 A (threonine to alanine) and S45N (serine to asparagine).
  - A group distinguished by four mutations all in antigenic regions, which includes some of our recent local specimens.
  - The largest group is distinguished by four additional mutations. Also the largest observed last season. This group is geographically diverse, and displaying additional mutations and bears continued surveillance.
- For space reasons, where multiple strains were 100% homologous and from the same country or state, one representative was chosen and the total noted to the right.

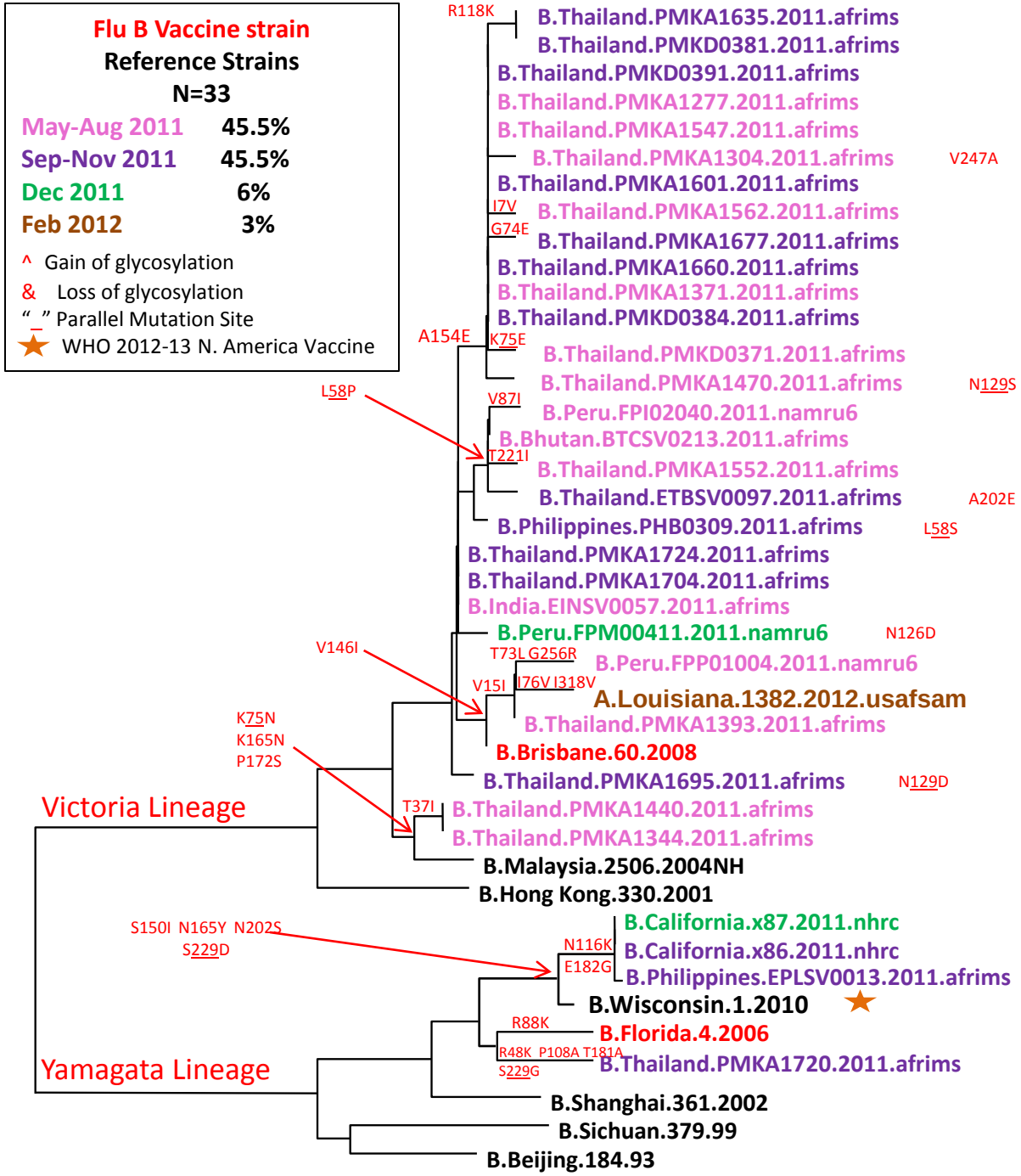
Source: USAFSAM/PHE (2510 5th Street, Wright-Patterson Air Force Base, OH 45433)



Influenza B HA (HA1) Phylogenetic Analysis 2011-2012

- 12% Yamagata lineage strains characterized (n=4/33) including a CONUS strain in Florida collected as recent as 6 December 2011.
  - 97.9% - 98.5% homology with previous B/Yamagata vaccine strain, B/Florida/4/2006-like virus
  - One parallel mutation sites, S229D/G (serine to aspartic acid/glycine)
- 88% Victoria lineage strains characterized (n=29/33)
  - 98.5% - 99.7% homology with B/Brisbane/60/2008-like virus
  - Main clade distinguished from B/Brisbane/60/2008-like virus by I146V (isoleucine to valine) and A154E (alanine to glutamic acid)
  - Three parallel mutation sites: L58P/S (lysine to proline/serine), K75E/N (lysine to glutamic acid/asparagine) and N129D/S (asparagine to aspartic acid/serine)

Source: USAFSAM/PHE (2510 5th Street, Wright-Patterson Air Force Base, OH 45433)



USAFSAM - Vaccine Effectiveness

(All Beneficiaries – Preliminary Estimates)

		OR_{crude}	N_{crude} [1]			VE_{crude}% (CI)	$OR_{adjusted}$	$N_{adjusted}$ [1]			$VE_{adjusted}$% (CI)
			N_{crude}	Cases	Controls			$N_{adjusted}$	Cases	Controls	
All beneficiaries	**All influenza viruses**										
	Overall	**0.66**	**671**	108	563	**33.7 (-2.1, 56.9)**	**0.48**	**652**	103	549	**51.8* (21.5, 70.4)**
	TIV[2]	**0.55**	**426**	68	358	**45.0* (6.4, 67.3)**	**0.41**	**415**	65	350	**58.6* (24.9, 77.2)**
	LAIV[3]	**0.87**	**419**	80	339	**12.7 (-42.1, 46.4)**	**0.71**	**407**	76	331	**29.4 (-24.9, 60.1)**
	Influenza A/H3										
	Overall	**0.74**	**650**	87	563	**25.88 (-19.6, 54.1)**	**0.56**	**631**	82	549	**44.0* (3.7, 67.5)**
	TIV[2]	**0.63**	**412**	54	358	**36.8 (-12.2, 64.7)**	**0.48**	**401**	51	350	**52.0* (7.6, 75.0)**
	LAIV[3]	**0.96**	**402**	63	339	**4.0 (-64.5, 44.0)**	**0.84**	**390**	59	331	**15.9 (-59.1, 55.5)**
Active Duty	**All influenza viruses**										
	Overall	**0.57**	**403**	68	335	**42.6 (-14.2, 71.2)**	**0.57**	**397**	67	330	**43.0 (-22.4, 73.4)**
	TIV[2]	**0.47**	**205**	33	172	**53.4 (-2.0, 78.7)**	**0.46**	**203**	33	170	**54.5 (-8.2, 80.9)**
	LAIV[3]	**0.70**	**243**	48	195	**30.5 (-43.5, 66.4)**	**0.74**	**238**	47	191	**26.5 (-77.3, 69.5)**
	Influenza A/H3										
	Overall	**0.71**	**391**	56	335	**29.1 (-63.2, 69.2)**	**0.62**	**391**	56	335	**37.6 (-39.6, 69.9)**
	TIV[2]	**0.52**	**199**	27	172	**48.5 (-21.4, 78.1)**	**0.59**	**197**	27	170	**41.0 (-51.1, 77.0)**
	LAIV[3]	**0.75**	**234**	39	195	**25.2 (-66.3, 66.3)**	**0.95**	**229**	38	191	**5.2 (-148.6, 63.8)**

* CI does not include 0 (i.e. statistically significant); positive VE indicates protective effect

[1] $N_{adjusted} \neq N_{crude;}$ removed if missing data for adjusted variable (gender)

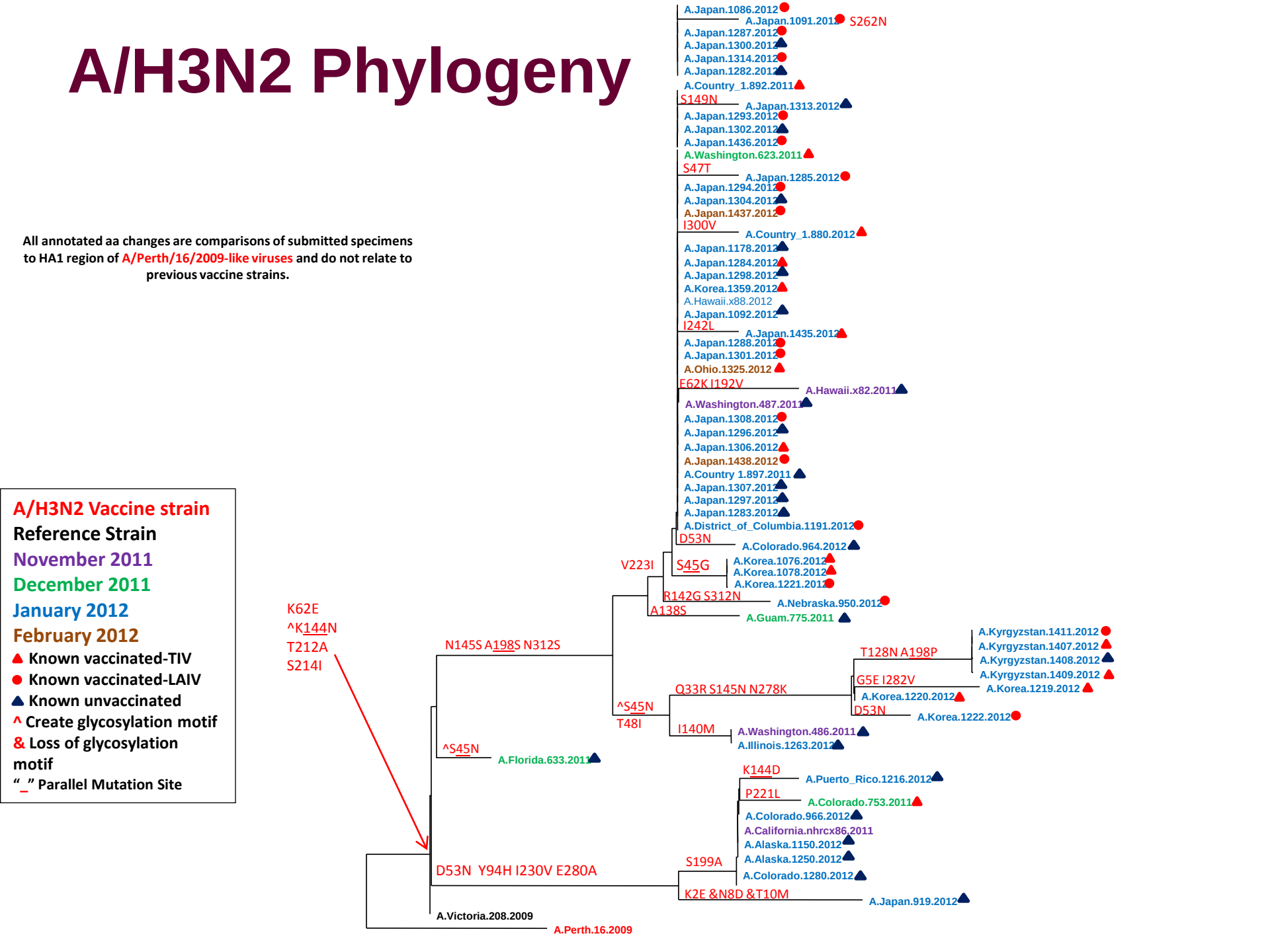
[2] TIV-specific estimates exclude cases and controls vaccinated with LAIV or unknown vaccine type.

[3] LAIV-specific estimates exclude cases and controls vaccinated with TIV or unknown vaccine type.

Logistic regression models performed, adjusting for gender & age group, VE determined as (1-odds ratio) (Eick et al, 2009 Vaccine)

A/H3N2 Phylogeny

All annotated aa changes are comparisons of submitted specimens to HA1 region of A/Perth/16/2009-like viruses and do not relate to previous vaccine strains.



AFHSC and USAFSAM Collaboration

DoD Active Component: 2010-2011

Vaccine Effectiveness (VE) by Subtype: 2010-11 TIV and LAIV					
Subtype	Vaccine	Cases, n (%)	Controls, n (%)	Odds ratio (95% CI)	VE (95% CI)
pH1N1	TIV	21 (33.4)	78 (32.2)	1.28 (0.52-3.15)	-28% (-215 to 48)
	LAIV	32 (54.5)	122 (50.4)	1.39 (0.57-3.40)	-39% (-240 to 43)
	None	8 (13.1)	42 (17.4)	Ref	Ref
A/H3	TIV	20 (26.0)	94 (30.6)	0.40 (0.18-0.88)	60% (12 to 82)
	LAIV	39 (50.6)	178 (58.0)	0.46 (0.22-0.96)	54% (4 to 78)
	None	18 (23.4)	35 (11.4)	Ref	Ref
B	TIV	7 (21.2)	39 (29.5)	0.36 (0.06-2.35)	64% (-135 to 94)
	LAIV	22 (66.7)	82 (62.1)	0.74 (0.21-2.54)	26% (-154 to 79)
	None	4 (12.1)	11 (8.3)	Ref	Ref

Methodology similar to: Johns MC et al, PLoS One 2010;19;5(5)
Current publication pending

Serologic Study

(Study Design)

- Subjects: recruits in ~week 5 of training (enrolled during March, flu weeks 9-12)
- Enrollment: n = 540 (MCRD-PI: 259, Ft Jackson: 201, Cape May: 80)
- Clinical data entered into database
  - 171 had subjective fever + either cough or sore throat
  - 260 reported no fever, no influenza vaccination previous yr
- Samples
  - Post-vaccine samples obtained
  - Pre-vaccine samples identified by DoDSR
  - Baseline sera ~133 days pre-vaccinations
- Serology reagents 2010-11 WHO Influenza Regent Kit
- Antiserum to A/2011-pH1N1 strain generated in ferrets

Faix, et al. Decreased serologic response in vaccinated military recruits during 2011 correspond to genetic drift in concurrent circulating pandemic A/H1N1 viruses. Submitted.

Serologic Responses in Vaccinated Recruits

measured by microneutralization assay, TIV-vaccinated (n = 64)

Virus	A/CA/7/2009 (H1N1)	A/Perth/16/2009 (H3N2)	A/CA/17/2011 (H1N1)
# Pre-vac. Titer≥40 (%)	10 (16%)	19 (30%)	5 (8%)
GMT pre-vac. (95% CI)	9.7 (7.6-12.4)	18.0 (14.0-23.0)	7.5 (5.8-9.5)
# Post-vac. Titer≥ 40 (%)	47 (73%)	62 (97%)	39 (61%)
GMT post-vac. (95% CI)	77.9 (56.5-107.4)	227 (165.0-313.8)	39.4 (28.5-54.3)
Seroconversion (%)*	47 (73%)	54 (84%)	41 (64%)
Fold change (95% CI)**	5.6 (4.1-7.6)	10.2 (7.6-13.8)	3.4 (2.5-4.7)

CI, confidence interval; GMT, geometric mean titer
*Seroconversion is defined as a four-fold increase in titer from pre-vaccine to post vaccine
**Fold change adjusted for pre-vaccine seroprotection

Seroconversion Rates in Naïve Subjects

(Initial Titers <40)

	TIV	LAIV	P Value
A/H3N2	98%	57%	P < 0.0001
A/H1N1(2009)	74%	43%	p = 0.0007
A/H1N1(2011)	64%	30%	p < 0.0001
Any Virus	77%	43%	p < 0.0001

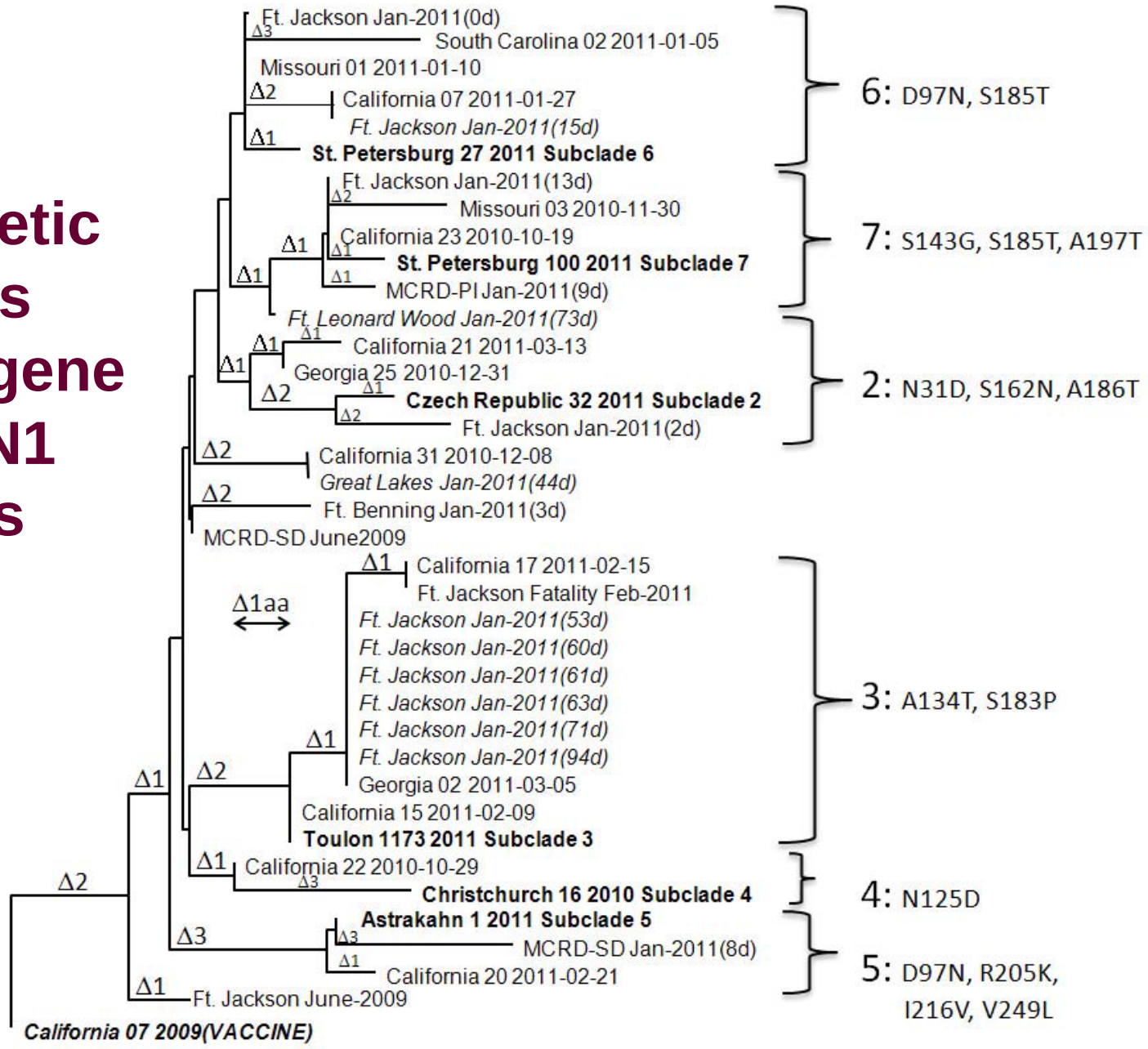
Serology Findings

(1) TIV induced greater total serum antibodies, and a more mature antibody response than LAIV.

(2) LAIV and TIV responses to 2011 pH1N1 were significantly lower than those against the 2009 pH1N1 strain.

(3) HA1 sequence analysis from concurrently circulating pH1N1 strains in 2011 demonstrated that a single clade with moderate drift from the pH1N1 vaccine strain and possessing the S183P mutation was responsible for the outbreak (next slide).

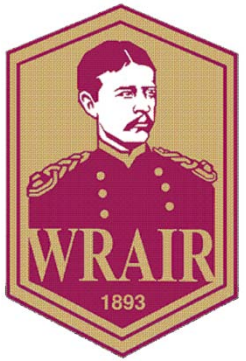
Phylogenetic analysis of the HA gene of A/H1N1 isolates



Summary

- **The DoD maintains a robust surveillance system with capacity to assess mid-season and end-of-season VE and molecular characterization of circulating viruses**
- **Recent increase (A/H3) among US military beneficiaries; low influenza activity at most overseas laboratories**
- **Molecular analysis indicates improved matching with WHO recommended 2012-2013 vaccine components**
- **Evidence of regional genetic drift for some A/H1N1 viruses resulting in decreased serum antibody matching and potential decreased VE**

A Global Laboratory Network



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Questions

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